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SECTION OF GEOLOGY AND MINERALOGY

MARINE SEDIMENTS AND PLEISTOCENE CHRONOLOGY

By WILLIAM D. URRY*

The sediments covering the floor of the great ocean basins, beyond the continental shelves, are accumulating at an exceedingly slow rate. Consequently, a few feet of these deposits often provide a continuous record of the history of terrestrial events that have occurred within the last million years. Under special conditions, the period may be much longer, extending perhaps over a considerable portion of Tertiary time, though the record is likely to be discontinuous.

Several ingenious methods[1] of securing vertical sections of the abyssal sediments, in the form of cores, are in general use. Examination of many such cores reveals the fact that, probably in the majority of cases, an excellent record of earth history is preserved undisturbed by the many processes that obliterate the details of similar records on land. There seems to be no reason why an intensive study of the ocean floor should not yield the full chronological story of the glacial period of the Pleistocene, the most recent period of the earth's history, but one still full of unsolved and intriguing problems.

* Geophysical Laboratory, Carnegie Institution of Washington, Washington, D. C. This lecture, illustrated by lantern slides, was presented at the meeting of the Section on December 1, 1947.

Concerning the last glacial stage, and its sub-stages—the Wisconsin of North America—the geologist has amassed a considerable body of facts, largely because it was an event of but yesterday reckoned in geological time. Nevertheless, the estimates of the chronology of even such recent events are confusing, at least in North America. This has serious repercussions in other fields of study, as, for example, in the story of man in the Western Hemisphere. Prior to the last glacial stage, the earth was subjected to great advances of ice on at least three consecutive occasions. Concerning the details, particularly the chronology, of these earlier glacial stages and the intervening warm spells, much of our knowledge is conjectural.

While the principal purpose of this presentation is to draw attention to a method of measuring time in the ocean sediments, any description would offer barren reading without reference to the methods, results, and conclusions of researchers in several branches of the geologic sciences, whose studies are, of course, the very essence of the problem in that they provide the evidence of changing conditions in the deposition of the sediments. There would be little incentive to measuring time in a sediment if it exhibited no distinctive changes in the past. Fortunately, nearly all cores of deep-ocean sediments are truly rich in events.

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Often, as in the suite of North Atlantic cores secured by Doctor C. S. Piggot,[2] the lithologist is able to distinguish buried zones of glacial marine débris interbedded with oozes characteristic of warm surface waters, or zones in which, for example, the incorporation of volcanic glass shards is a distinctive feature. Lacking any such immediately apparent evidence of changing conditions, it may still be possible to obtain a detailed picture of past climatic changes, as in sediments consisting almost wholly of foraminifera and cementing clay. Doctor J. A. Cushman's work[3] on the globigerina oozes of the Caribbean Sea is an excellent example. Studies of the faunal distribution of many other types of fossils in the ocean bottom have also proved highly productive of evidence for changes in the past.

The comprehensive studies of deep-sea cores[4] performed and documented by members and co-workers of the United States Geological Survey constitute an excellent pattern for guiding future work; and, highly detailed as these studies may appear to be to the reader, much of the spade work cannot be neglected if we are to benefit fully from the wealth of information available at the bottom of the ocean. These researches standing alone are highly important, but they acquire added significance if a sound basis can be established for correlation from place to place, from land mass to land mass, from hemisphere to hemisphere. Most assuredly, this correlation cannot be based on a spatial dimension such as depth, any more than such a yard-stick is of use on land. This is quite obvious from an examination of the lithology of cores from even a very limited area like the western basin of the North Atlantic.

The major problems of the Pleistocene necessarily involve all the great ocean basins. The only dimension that can form a true basis for correlation is that of absolute time. Estimates of the rate of deposition, determined by subjective methods, have appeared in the literature[5] and are in substantial agreement with rates determined by the presently described objective procedure in the order of magnitude of the grand averages. Nevertheless, the rate of deposition has been so variable from place to place and time to time that nothing but confusion could result from using such results to date a specific event in the sediment.

As is the case in many researches, the initial results which pointed the way to a method of measuring time in the ocean sediments were incidental to the problem. Piggot and Urry[6] were searching for an explanation of certain phenomenally high radium contents in grab samples collected on the last cruise of the *Carnegie*.[7] To this end, the radium content of small in-

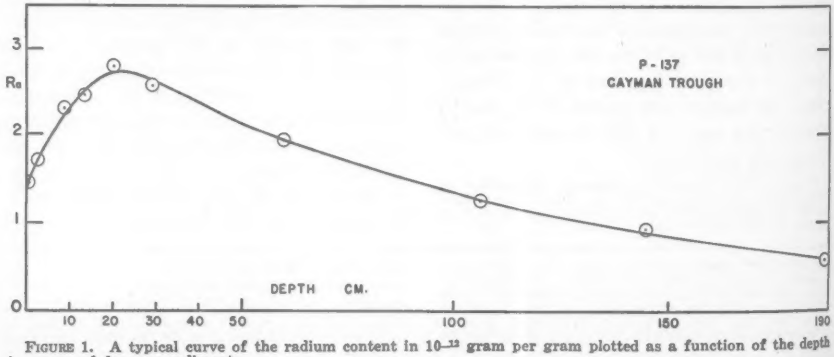

FIGURE 1. A typical curve of the radium content in 10^{-12} gram per gram plotted as a function of the depth in a core of deep-sea sediment.

crements of deep-sea cores was being measured. FIGURE 1 illustrates a curve of the radium content as a function of depth in a core that has proved to be typical of the sediments in some fifteen cores from the Ross Sea to the North Pacific and from the Caribbean to the North Atlantic. Naturally, there are minor variations that depend on the type of sediment and particularly on the span of time represented by the core.[8] It is now established that the high radium content in the surface of many deep-ocean sediments is a transitory feature. There appears to be only one plausible explanation of such a specific picture of the variation of radium content with depth in the deposits of the deep ocean.

The peculiar features of a maximum and the eventual establishment of a low and constant radium content[9] (not to be seen in FIGURE 1 but observed in the lower half of several cores from the Pacific Ocean) receive a complete explanation if, during the course of their deposition, the sediments exhibit a preference for certain members of the uranium family.

In old radioactive minerals, the relative amounts of the various members do not change with time; they are in radioactive equilibrium. Were one to save all the separations of a chemist's analysis of an old pitchblende and request posterity to study the portions from time to time for the next half-million years, the final result would be characteristic of what one finds in the ocean sediments, particularly for the rare-earth fraction which would contain ionium, the immediate parent of radium. The original radium would have been separated from its parent but new radium would accumulate in the ionium fraction until, in 10,000 years, radium and ionium would again be in equilibrium. Thereafter, the radium content of the ionium fraction would decrease, but only so fast as its parent decays, which is at the rate of one-half every 82,000 years. It is quite practical to follow such a decrease for five half-lives, even with extremely small concentrations, and thus posterity would have a clock that would not run down for close to half a million years. In studying the uranium fraction of the chemist's separation, it would be found that the ionium content, and with it the radium content, was continuously increasing until after half a million years no further change occurred. Uranium decays so slowly and is present in such prodigious amounts compared with its daughter elements that the supply is virtually inexhaustible for our purpose.

In the ocean bottom, nature is a poor substitute for the chemist and the separations are only partial. The sediments exhibit a decided preference for ionium and are non-committal about radium, while showing a great but not complete dislike for uranium. It is on account of the incompleteness of this dislike that the radium content of the ocean sediment does not decrease to zero, and this property is fully utilized in determining the uranium content from the radium measurement wherever the sediment represents a span of time greater than half a million years.

Such a theory to account for all the details of the variation of the radium content in the bottom sediments receives substantial support in studies of the radioactivity of sea water.[6] Here, one finds the exact counterpart of the condition of deficiency of uranium with respect to equilibrium with radium (and ionium) obtaining in the surface of the ocean bottom: the ocean waters possess a uranium content greatly in excess of that necessary to support the radium through its parent, ionium.

Because of the partial nature of the separations of the radioactive elements in the surface of the sediments, the mathematically possible paths by which the radium content can reach a state of equilibrium are many and tortuous. Nevertheless, with the aid of the equations governing the growth and decay of the

radioactive elements, it is relatively easy to follow them all.[10]

It is apparent, then, that the deep-ocean sediments possess a built-in clock which we are at liberty to employ with one further assumption, namely, that the sediment at the location of any given core has always acquired, at the time of its deposition, a constant amount of the radioactive elements. This appears to be a drastic assumption, but there is much evidence to support it. For example, measurements of the uranium content made independently of the radium determinations have shown a constant uranium content throughout a core—a core that exhibited a variation of the radium similar to that shown in FIGURE 1. Furthermore, the flat tails of five curves of radium content against depth show no tendency to wiggle, indicating that the uranium content acquired over long periods, as much as 500,000 years in one case, was very constant. This latter analysis can, of course, be made only when the sediment represents a span of time greatly in excess of 400,000 years.

Application of this clock to the dating of events in marine sediments has, as yet, produced little more than the signs pointing to the possibilities. In the North Atlantic, where rates of deposition have been high, a core ten feet in length covers little more than the Wisconsin Glacial Stage. It has proved possible to date, and to correlate on this basis, the changes in the sediments of the North Atlantic which represent the equivalent of the four substages of the Wisconsin ice on land. It also has been possible to establish a chronology of the climatic changes that occurred during and following the glacial sub-stages and to date the "climatic optimum" of post-glacial time as indicated by the relative abundances of various types of foraminifera. Many of the changes associated with the North Atlantic sediments proved to be contemporaneous with effects arising from a common cause to be expected on land, provided the estimates of the subjective methods of measuring time in glaciated regions are accepted.

While the longer cores from the North Atlantic reached back no more than 70,000 years, even short cores from the Bartlett Deep in the Caribbean Sea were found to represent a span of 200,000 to 300,000 years. The relative abundances of the foraminifera in two such cores, which presumably indicate the climatic changes at the surface of the Caribbean Sea, exhibit a good correlation based on the dating but no correlation on the basis of depth because of the different rates of deposition. Both cores show that the periods of warm and cold surface waters are contemporaneous with the rise and fall of the snow-line level in the Alps, although no detailed comparison of the chronology of the European and North American glaciation is possible as yet. A detailed analysis of the foraminifera near the top of one core from the Caribbean Sea was completed, and periods of cold and warm surface water appear to exhibit a chronological correspondence with the alternating zones of glacial marine débris and warm water deposits in the dated cores of the North Atlantic. A full discussion of these results and an acknowledgment of the cooperative efforts of many researchers have already been published.[8]

From these beginnings, it appears that the effects of glaciation over widely separated areas of the northern hemisphere are roughly contemporaneous. Our present knowledge of the chronology of the effects of glaciation in the southern hemisphere, particularly with reference to the date of any specific event in the northern hemisphere, is purely conjectural. Very recently, curves of the radium content as a function of depth have been constructed for several cores collected by Dr. J. L. Hough on board the U.S.C.G.C. *Northwind* with the Navy Antarctic Expedition of 1946-47. These cores are all from the southern hemisphere from just south of the

Equator to the Ross Sea. With the completion of the necessary lithological and foraminiferal studies, it should be possible, in the near future, to provide a preliminary answer to the outstanding question of glaciology—Is the glaciation contemporaneous in the northern and southern hemispheres?

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SECTION OF BIOLOGY

December 8, 1947

SYMPOSIUM: EFFECT OF DERIVATIVES OF FOLIC ACID ON CERTAIN TYPES OF NEOPLASTIC DISEASE

INTRODUCTION TO THE CHEMISTRY AND ACTION OF CERTAIN PTEROIC ACID DERIVATIVES

By COY W. WALLER*

On May 29, 1946, a series of papers[1] was presented before this Academy on the isolation, characterization, synthesis, and action of pteroylglutamic acid. The genesis of pteroylglutamic acid has been reviewed[2] and will not necessarily be given here; however, the origin of the chemical work presented at that meeting was also the beginning of the work to be presented at this time.

In 1942, when Dr. Brian L. Hutchings began work at the Lederle Laboratories, the investigations on folic acid in a number of widely separated fields were converging. Dr. Hutchings began by making a concentrated effort to find new sources for folic acid materials which would result in increased yields over the existing sources. The need for a better source of folic acid was obvious since only about 100 milligrams of the vitamin could be obtained from a ton of pig livers and about 300 milligrams from a ton of horse livers.

In the course of his work, Dr. Hutchings investigated a large number of molds as sources for the growth factor. Among these was the mold used to produce riboflavin. Assays were run on the filtrates from riboflavin tanks after the flavin had been removed. Fortuitously, the filtrate from one of these tanks contained considerable quantities of a growth factor when tested microbiologically, using *L. casei*, while filtrates from other batches of riboflavin did not exhibit any such growth stimulation. Immediately, a contaminant was suspected. A bacillus was isolated from the riboflavin tank and two bacilli were collected on agar plates exposed in the riboflavin plant. However, of the three possible contaminants only one of the bacilli produced much of the growth factor; this bacillus was isolated from the exposed agar plate. The growth factor produced by this bacillus was subsequently found to be different from the liver factor and was named the fermentation *L. casei* factor.[3]

The bacillus producing the fermentation *L. casei* factor was, of course, investigated extensively. It is an unidentified member of the genus *Corynebacterium*. Its nutritional and growth habits were determined, and soon production of research quantities of the factor was under way.

The investigation of the fermentation *L. casei* factor is now published history. Degradation[4] has shown it to be pteroyltriglutamic acid. The liver factor has been shown to be pteroylglutamic acid.[5] Pteroylglutamic acid has been synthesized[6] and placed on the market as a hemopoietic agent. The synthesis of pteroyltriglutamic acid by Dr. Boothe and co-workers will be presented in the following paper.

Soon after the isolation of the fermentation *L. casei* factor at Lederle, a request for some folic acid was received from Dr. Richard Lewisohn of Mount Sinai Hospital. Dr. Lewisohn and his co-workers had under way an extensive program of testing for regression of tumors in mice.

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Up to that time, the best results had been obtained with spleen and yeast extracts. The results suggested that some member of the vitamin B complex might be the responsible factor. The fermentation *L. casei* factor was supplied to this group of workers. In 1944, Leuchtenberger, Lewisohn, Lazlo, and Leuchtenberger[7] reported that the factor inhibited the growth of Sarcoma 180 transplanted in female Rockland mice. In a later publication,[8] it was shown that pteroylglutamic acid had no therapeutic effect on spontaneous breast tumors in mice, while the fermentation *L. casei* factor, pteroyltriglutamic acid, caused complete regression in 30 to 40 per cent of tumors in the animals. These findings have served as an impetus to the synthesis and to the clinical testing of pteroyltriglutamic acid. Some of the clinical findings will be presented in this series of papers by Dr. Klainer as well as by Dr. Lehv.

The antagonism between compounds promoting growth and those which inhibit growth has received ever increasing attention since Woods[9] described the interference of *p*-aminobenzoic acid on the action of sulfonamide. The research program at Calco and Lederle has involved the preparation of a number of analogues and homologues of pteroic acid. Some of these compounds possessed growth stimulation for the test organisms and animals, while others have actually inhibited the growth response of pteroylglutamic acid in the biological systems.

Recently, Hutchings and co-workers[10] reported the synthesis and inhibitory action of pteroylaspartic acid. This was the first purified and fully characterized derivative of pteroic acid to be described which had anti-pteroylglutamic acid action. More recently, Seeger and co-workers[11] reported the synthesis of a purified 4-amino- derivative of pteroylglutamic acid. The purifications of these antagonists are extremely important, in spite of the difficulty this entails. It is known that condensations, such as used in the preparation of pteroylglutamic acid, produce crude products which often have both growth promoting and inhibiting substances.

Dr. Smith will present the synthesis of a group of purified antagonists which have been tested routinely at Lederle. The pathological and experimental work on chicken sarcoma will be presented by Dr. Woll and Mr. Little. Dr. Meyer will present his clinical findings on the use of certain of these compounds in human leukemia.

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SYNTHESIS OF PTEROLY-γ-GLUTAMYL-γ-GLUTAMYLGLUTAMIC ACID (TEROPTERIN)

By J. H. BOOTHE, J. H. MOWAT, B. L. HUTCHINGS, R. B. ANGIER, C. W. WALLER, E. L. R. STOKSTAD, J. SEMB, A. L. GAZZOLA, AND Y. SUBBAROW *

One of the simplest methods of synthesis of pteroylglutamic acid[1] involves the use of 2,4,5-triamino-6-hydroxypyrimidine, α, β-dibromopropionaldehyde and *p*-aminobenzoylglutamic acid. It was known that the fermentation *Lactobacillus casei* factor contained two molecules of glutamic acid[2] in addition to the one in pteroylglutamic acid, attached through peptide linkages. Therefore, the problem of synthesis of the fermentation *L. casei* factor was essentially to prepare a tetrapeptide consisting of one molecule of *p*-aminobenzoic acid and three molecules of glutamic acid. This could then, presumably, be used in the above reaction in place of the *p*-aminobenzoylglutamic acid.

Because glutamic acid has two carboxyl groups (known as the α or the γ carboxyl) there are two possible isomeric forms of a dipeptide of glutamic acid and five possible isomers of a tripeptide of 1(+)glutamic acid. This posed a problem as to which of the five isomers would correspond to the fermentation *L. casei* factor. The first indication as to which carboxyl group was involved in the peptide linkages was arrived at by synthesis of the two isomers containing two molecules of glutamic acid, *i.e.*, pteroyl-α-glutamylglutamic acid and pteroyl-γ-glutamylglutamic acid.

The former compound was synthesized by a general method first devised by Bergmann and Zervas.[3] 1(+)Glutamic acid was reacted with benzylchlorocarbonate to form carbobenzoxyglutamic acid, which was then treated with acetic anhydride to form carbobenzoxyglutamic anhydride. This anhydride was reacted with diethyl glutamate to yield diethyl carbobenzoxy-α-glutamylglutamate. The ester groups were removed by hydrolysis in dilute sodium hydroxide and the carbobenzoxy group was removed by hydrogenation in the presence of 10 per cent palladium-charcoal catalyst to yield α-glutamylglutamic acid. This dipeptide was then reacted with *p*-nitrobenzoyl chloride in a Schotten-Baumann type reaction to form *p*-nitrobenzoyl-α-glutamylglutamic acid. This nitro compound was reduced to the corresponding amino derivative by hydrogenating with platinum oxide and then reacted with 2,4,5-triamino-6-hydroxypyrimidine and α,β-dibromopropionaldehyde to form pteroyl-α-glutamylglutamic acid.

The γ-linked isomer was prepared by first reacting the carbobenzoxyglutamic anhydride already mentioned with ethanol at 120° C. to obtain α-ethyl carbobenzoxyglutamate.[4] This *mono* ester was treated with phosphorous pentachloride to form the acid chloride[5] and then with diethyl glutamate to yield triethyl carbobenzoxy-γ-glutamylglutamate. The carbobenzoxy group was reduced off as previously described and the triethyl γ-glutamylglutamate was isolated as the hydrochloride. This dipeptide was *p*-nitrobenzoylated in a Schotten-Baumann reaction which at the same time hydrolyzed the ester groups to yield *p*-nitrobenzoyl-γ-glutamylglutamic acid. The nitro group was converted to the amino group by hydrogenation using platinum oxide catalyst and was then condensed with 2,4,5-triamino-6-hydroxypyrimidine and α,β-dibromopropionaldehyde to yield pteroyl-γ-glutamylglutamic acid.

Comparison of the biological data of the two isomeric pteroyldiglutamic acids is shown as follows:

	S. faecalis R.	*L. casei*
Pteroyl-α-glutamylglutamic acid	0.5–1%	0.5–1%
Pteroyl-γ-glutamylglutamic acid	60–70%	60–70%
Pteroylglutamic acid	100%	100%

Since the α isomer showed a very low microbiological activity and the γ isomer

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a relatively high activity, it was thought that, probably, the three glutamic acids in the fermentation *L. casei* factor were connected through the γ carboxyl groups. Therefore, the γ-linked tripeptide was prepared through the following series of reactions.

Triethyl-γ-glutamylglutamate, described above, was reacted with the acid chloride of α-ethyl carbobenzoxyglutamate to yield tetraethyl carbobenzoxy-γ-glutamyl-γ-glutamylglutamate. The carbobenzoxy group was removed by hydrogenation with palladium-charcoal catalyst and the resulting tripeptide treated with *p*-nitrobenzoyl chloride in benzene in the presence of diethyl amine. The resulting *p*-nitrobenzoyl tripeptide was then reduced to the corresponding *p*-amino derivative and condensed with α,β-dibromopropionaldehyde and 2,4,5-triamino-6-hydroxypyrimidine to form the pteroyl derivative. This pteroyl-γ-glutamyl-γ-glutamylglutamic acid showed the same microbiological activity as the fermentation *L. casei* factor:

	L. casei	*S. faecalis R.*
Synthetic compound	60%	2.0–6.0%
Natural compound	60%	2.0–6.0%

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A CASE REPORT OF METASTATIC CARCINOMA TREATED WITH TEROPTERIN*

By MAX J. KLAINER†

The clinical management of patients with metastatic carcinoma has always presented difficult problems to the practicing physician. Not only have these cases invariably been fatal, but, in addition, the patient has all too frequently suffered great pain and has required considerable nursing care. It is, therefore, of great interest to report a case of metastatic carcinoma in whom not only the suffering was eliminated, but who has been restored to a life of utility by the use of a new chemotherapeutic approach.

Case Report. This patient, a 39-year-old Armenian housewife, was first seen in February, 1947, because of severe, agonizing pains originating in the region of the lower spine and radiating down the posterior aspect of the left thigh and left leg to the heel. A right radical mastectomy had been performed (by Dr. D. Richard Miller) at the Massachusetts General Hospital, Boston, in December, 1944, because of an adenocarcinoma. At the time of surgery, axillary nodes were found and removed. Pathological study reported grade III. The patient had made a good recovery from the operation and had done well until March, 1946, when pain developed in the region of the mid-lumbar spine. X-ray studies revealed a destructive process in the third lumbar vertebra. The patient then was given radiotherapy over a period of several months without any appreciable improvement. X-ray studies repeated in September, 1946, showed extension of the process in the third lumbar vertebra and new areas of destruction in the dorsal vertebrae and the ribs. A diagnosis of metastatic carcinoma was made and the patient placed on narcotic medication for relief of pain. However, she became progressively worse and soon was bed-ridden. She was unable to make the slightest movement without severe pain.

The patient's condition seemed hopeless and she was hospitalized primarily for the purpose of being kept as comfortable as possible. On admission to the New Eng-

* Teropterin is the name given by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, for pteroyltriglutamic acid.

† Stoneham, Massachusetts.

land Sanitarium and Hospital, Stoneham, Massachusetts, the patient proved to be a trying nursing problem.* Only by lying quietly on her right side with her knees drawn to her abdomen could she endure her pain. Changing the bed linen, bathing, and the use of the bedpan were almost impossible. In addition, she sweated profusely, necessitating frequent changing of the bed linen. One hundred mg. demerol and dilaudid in doses of grains 1/16 every 4 hours only partially checked her pain.

Physical examination at the time of admission to the hospital revealed percussion tenderness along the lower dorsal and lumbar vertebrae and along the course of the left sciatic nerve. The eyes, ears, nose and throat, lungs, heart, and upper extremities were all within normal limits. The blood pressure was 140 mm. of mercury systolic and 90 diastolic, temperature 98.6, pulse 100, respiration 20 per minute.

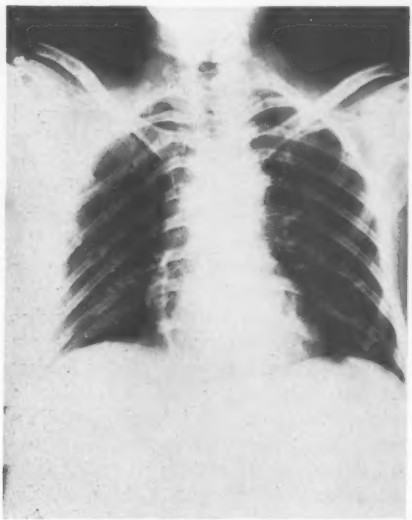

FIGURE 1.

Initial laboratory studies disclosed the following: hemoglobin, 12 g. (77 per cent) Sahli; red blood count, 3,660,000; white blood count, 5,450 with 40 per cent polymorphonuclears and 58 per cent lymphocytes. The total serum protein was 6.3 grams with 3.0 grams albumen and 3.3 grams globulin. No Bence Jones protein was found in the urine, and the urinalyses were not otherwise remarkable. In spite of extensive bone destruction, the acid phosphatase was essentially normal, 4.5 King units.

X-ray films of the dorsal and lumbar spine, ribs, and pelvis showed innumerable areas of bone destruction with pathological fractures of several of the ribs and of the eighth dorsal and second and third lumbar vertebrae (FIGURES 1, 2, and 3). Areas

FIGURE 2.

of bone destruction were also found in the skull and in the right scapula. In an effort to check further bone destruction, the patient was placed on 150 mg. testosterone propionate given in 3 divided doses daily and 60 mg. teropterin, each being administered intramuscularly.†

During the first week of her hospital stay, the patient had her usual menstrual

* The author wishes to thank the medical and nursing staff of the New England Sanitarium and Hospital, whose help in the management of the case was of great value.

† Teropterin had been submitted for clinical study by Dr. Y. SubbaRow, Director of Research, and his staff at Lederle Laboratories Division, American Cyanamid Company, to Dr. S. Farber of the Children's Hospital, Boston. I wish to express my thanks to Dr. J. Hawkins, formerly associated with Dr. Farber, for our original supply of the drug.

FIGURE 3.

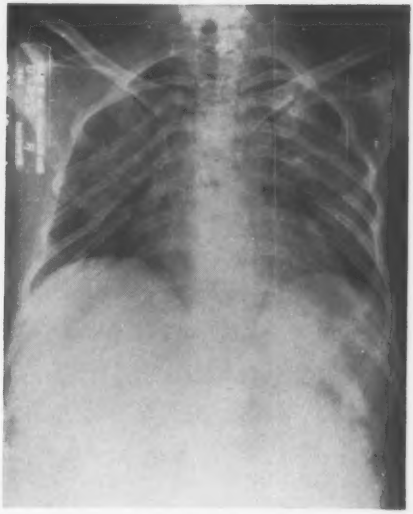

FIGURE 4.

FIGURE 5.

period, and with the onset of the menses the pain increased markedly. An oophorectomy appeared advisable, and this was performed successfully on March 3, 1947, by Dr. Raymond Auvil of the hospital staff. At the time of operation, the uterus was found to be enlarged, but there were no masses in the liver or elsewhere in the abdomen. Pathological studies of the removed tissues revealed negative Fallopian tubes, but sections of the ovaries showed foci of metastatic adenocarcinoma.

In the first two weeks following surgery, the patient showed little change and continued to require large doses of narcotics for relief of pain. During this time, however, the testosterone propionate was reduced to 100 mg. daily while the teropterin was continued at 60 mg. daily. On March 17, 1947, the patient was given a transfusion of 500 cc. of citrated blood with prompt return of the hemoglobin and red count to normal levels.

The first evidence of improvement was noted on March 19, 1947. The pain became less marked, the sweats were markedly reduced, and the patient became more cheerful. About March 23, she suffered a slight setback with accentuation of pain, but this was attributed to her expected menstrual period. Immediately thereafter, progressive and marked improvement was noted. By April 1, 1947 practically all narcotic medication for relief of pain was eliminated and the testosterone medication completely discontinued. The patient now received teropterin intramuscularly, and barbiturates were given for sedation and aspirin compound tablets for control of pain. During the period of testosterone therapy, this patient had developed secondary sex changes such as

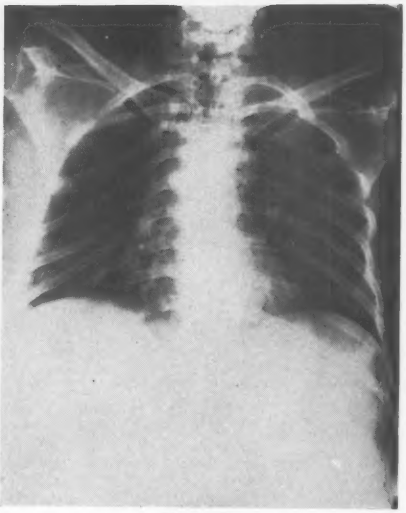

FIGURE 6.

FIGURE 7.

hirsutism and deepening of the voice, which, however, slowly disappeared upon discontinuance of this drug. On April 11, this patient, who on admission had been unable to move without pain, dangled in bed. On April 14, she sat up in a wheel chair.

Repeat x-ray studies of the involved bones done on April 20 were interpreted as follows: "Reexamination of the skeletal system shows no significant increase in the areas of bone destruction. As a matter of fact several of the previously described areas of bone destruction appear smaller and there is new bone formation seen in several areas where the destruction was markedly pronounced. Several of the pathological fractures show evidence of bony regeneration. The compression fractures of the second and third lumbar vertebrae are still present as previously described but the bone structure is somewhat denser" (FIGURES 4 and 5).

In May, 1947, the patient was measured for a back brace. On May 14, she was allowed to walk, first with the aid of a walker and then with a cane only. This increase in activity produced no increase

FIGURE 8.

in the small amount of residual discomfort, and on June 5, 1947, she was discharged home on a maintenance dose of teropterin 20 mg. b.i.d.

X-rays taken at the time of discharge were interpreted as follows: "Films of various bones show a remarkable change in the appearance of the bone structure with disappearance of many of the previously described areas of bone destruction with recalcification of the bone and healing of many of the fractures, particularly of the ribs. The bone structure of the

involved lumbar vertebrae has improved due to increased recalcification. The findings as a whole indicate a very marked improvement in the previously described findings of pathological fractures and metastases."

Since her discharge from the hospital, this patient has continued to improve both clinically and roentgenologically. Except for her back brace, she is now able to walk without the aid of any support and can perform many of her previous household duties. Except for transitory aching in the region of the left hip, which is readily relieved by an aspirin compound tablet, she is free of symptoms. The teropterin medication has been continued with a daily maintenance injection and she has learned to administer it herself. X-ray films that were taken in October, 1947, showed no new areas of bone destruction and further regeneration of bone formation in areas previously involved (FIGURES 6, 7, and 8).

The patient was last seen on December 1, 1947. At that time, she was completely ambulatory and was complaining only of mild aching in the lumbar spine on prolonged standing or walking.

Summary

In summary, a case has been presented of a 39-year-old woman with metastatic spread of an adenocarcinoma, presumably originating in the breast, in whom the combined use of oophorectomy, testosterone propionate injections, and teropterin injections produced definite clinical and roentgenological improvement. No claim has been made that teropterin alone produced the favorable results. However, the use of teropterin enabled the patient to discontinue the testosterone after the first month. Furthermore, it is interesting to note that the objective evidences of improvement, namely the x-ray changes, were not noted until several months after the oophorectomy and the discontinuance of testosterone therapy.

If the results obtained in this case were to be described in the manner in which surgeons commonly report their results in surgery on malignancies, it could be said that this patient with metastatic spread of a carcinoma to practically all her bones and to the soft tissues of the pelvis has, to date, obtained a 10-month "cure" by this combined chemotherapy and surgery.

USE OF TEROPTERIN IN NEOPLASTIC DISEASE: A PRELIMINARY CLINICAL REPORT

By S. P. LEHV, L. T. WRIGHT, S. WEINTRAUB, AND I. ARONS*

A preliminary clinical report is presented here on the use of teropterin in a series of cases of malignancy in Harlem Hospital. Since it is a preliminary report, we are confining ourselves to the presentation of our findings without attempting to interpret them or draw premature conclusions.

The study was started in August, 1947, by a group composed of Drs. Wright, Weintraub, Arons, and the writer. We confined our selection to those cases which were considered hopeless and terminal by virtue of extensive carcinomatosis beyond the reach of any of the other approved methods of therapy. In fact, our early cases were moribund. We felt that any favorable response in such cases would justify further study.

Accordingly, fortified by the original animal work of Lewisohn, Leuchtenberger, *et al.* [1, 2, 3] as well as the clinical observations of Dr. Farber's group[4] in Boston, teropterin therapy was instituted as a sole form of treatment. This was done to provide as controlled a study as possible.

* Departments of Surgery, Pathology, and Radiotherapy, Harlem Hospital, New York, N. Y. The teropterin used in these studies was supplied by Lederle Laboratories Division, American Cyanamid Company. The authors wish to thank Drs. E. B. Liggins and J. B. Shapse and Mr. H. Blechman for their assistance in this work.

With the exception of two cases where surgery and stilbestrol were used, respectively, the patients in our group were given no other form of therapy, excepting symptomatic routine medication. It must be remembered that we were dealing with adults, mostly middle-aged, and we met with the complications of intercurrent infections and the usual degenerative diseases.

Teropterin (Lederle) is a yellow powder. It is instantly soluble in normal saline, is apparently stable at room temperature, and is completely painless on injection. No toxic effects were noted in animals, none in the series of over one hundred cases in humans treated by the Boston group, and none in our series. The chemistry and pharmacology of teropterin need not be repeated here.

With the assurance given us by the above data, we did not hesitate to undertake this clinical study. Of thirty-three treated cases, we are reporting twenty which to this date have been observed for periods of from one to three months. The remaining cases have not been under our observation long enough to be included.

TABLE 1

TYPE AND LOCATION OF TUMOR

Carcinoma of prostate	4
Malignant lymphoma	1
Carcinoma of digestive tract	10
Malignant melanoma	3
Osteogenic sarcoma	1
Metastatic carcinoma of neck	1

METHOD OF STUDY. In addition to the customary work-up, the patients were observed for subjective and objective changes. The following studies were made in each case: x-ray studies, multiple biopsies, chemistry, and hematological values. The x-ray studies were made at approximately two-week intervals, the hematology was done weekly, and the chemistry weekly when abnormalities were found. Observation of the patient's activity was carefully noted together with the patient's own opinion of his progress.

The histological findings and x-ray studies will be given in a later report.

The following laboratory studies were made in each case:

(1) Urine analyses.
(2) Hematology: in the form of red and white blood counts and hemoglobin.
(3) Liver function tests:
    a. VandenBergh.
    b. Thymol turbidity.
    c. Bromsulfalein retention.
(4) Blood: creatinine, urea nitrogen, and glucose.
(5) Acid and alkaline phosphatase.
(6) Total protein and A/G ratios.
(7) Kahn test.

In this group of neoplasms, most of them far advanced, there was a conspicuous absence of markedly abnormal chemistry values. In a few of our cases where the liver was grossly involved with enormous palpable enlargement, the liver function tests were normal.

FINDINGS: *Urine Analyses.* No changes were noted during treatment.

Hematology. The red blood cell count and the hemoglobin values were watched closely because of the relationship between teropterin and folic acid. Occasional abnormalities in the white blood cell count were noted, which appeared as a diminution in the lymphocytes, both absolute and relative. Despite changes in the chemistry and clinical improvement in some patients, the red blood cell count and hemoglobin values were not appreciably affected. In some cases, supportive therapy was needed in the form of transfusions of whole blood and plasma.

Liver Function Tests. Of the twenty cases, only five were found that showed abnormal liver function. Of these, two showed improved excretion of bromsulfalein; one went from a 45 per cent retention to 30 per cent and the other from a 15 per cent retention to 0. Both died.

Alkaline Phosphatase. In our series, abnormalities were noted in eleven cases. Two cases showed values just above normal limits, a third showed no change after one month's treatment, the fourth in-

creased after two months' treatment, and the fifth dropped from 17.7 Bodansky units to 6.1, but then became elevated to 17.7 just before death. The remainder of the cases showed a decrease. In compilation, therefore, nine cases showed no abnormalities, and, of the remaining eleven, six improved and five are more or less indeterminate.

Acid Phosphatase. These data are considered insufficient, but, for the purpose of record, are reported. In four cases of prostatic cancer, we noted in one (W.D.) a temporary rise from 10.6 to 21.8 and then a fall to 0.25 after one month's treatment. The alkaline phosphatase in this case fell from 22.2 to 16.9 in the same length of time. The second case (E.G.) showed a drop from 16.8 to 8.2 in the acid phosphatase, while the alkaline phosphatase remained at a high normal level. The third (D.K.) demonstrated a relatively normal acid phosphatase reading—6.03—but a high alkaline phosphatase of 40.0. Within five weeks after treatment was instituted, the alkaline phosphatase in this case came down to 24.8 and the acid phosphatase to 1.7. In this same patient,

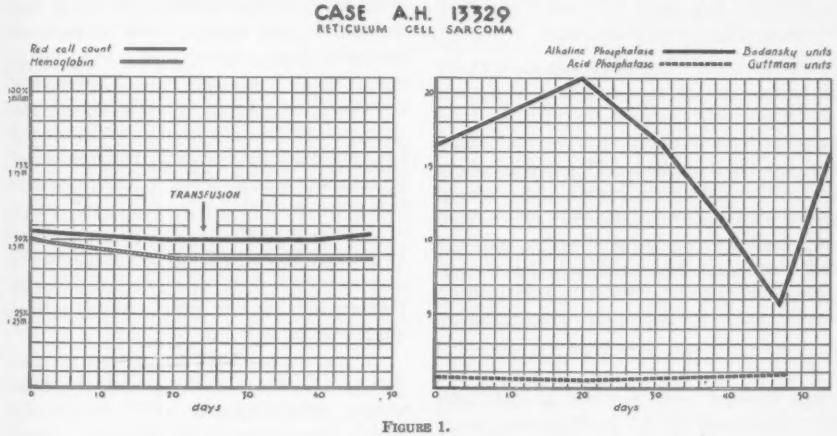

FIGURE 1.

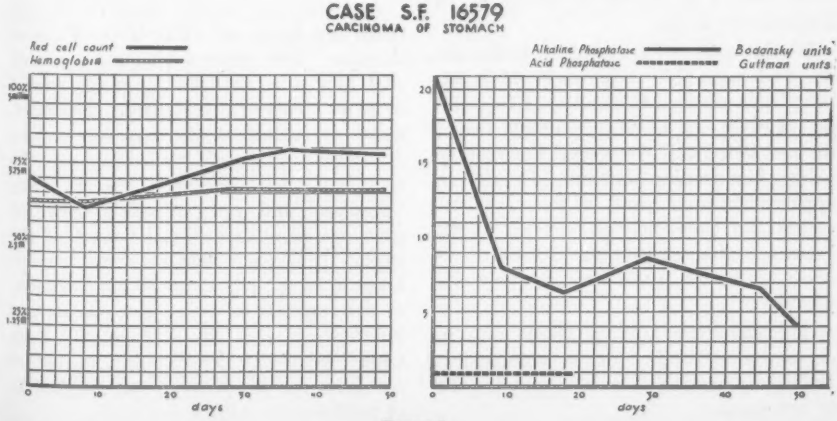

FIGURE 2.

it was noted that liver function tests were normal; the bromsulfalein retention was 0, the thymol turbidity stayed within the range of 2-3, and the VandenBergh gave a negative direct reaction. The fourth case showed no change in the acid phosphatase, which remained at a low level, but did show a drop in the alkaline phosphatase from 15.3 to 4.0 after six weeks of treatment.

The other blood and chemistry values were taken to help us in clinical management and evaluation.

FIGURES 1 and 2, taken from the cases of patients A.H. and S.F., are illustrative of our findings in two instances.

DISCUSSION. It would appear that, by virtue of the lack of consistently abnormal chemical and hematological findings, we cannot depend upon those values alone for prognosis and should consider them with caution as a diagnostic aid. We do feel that, in a few cases, they have given us a lead as to general progress, and the fall in alkaline and acid phosphatase has paralleled general clinical improvement.

It is true that, in those cases where no improvement was noted in the chemical values, the patients died. Some of the cases showed improvement in chemistry but died nevertheless. Furthermore, many cases showed no abnormal values at all from start to finish.

We have been impressed with the absence of hematinic response in those patients who received treatment. In a number of cases, we found a moderate rise in the red blood cell count and hemoglobin values, but nothing startling. Despite an apparent improvement in the chemistry values and liver function, as well as the assurance of these very patients that they never felt better, it was necessary to transfuse them.

The chemistry findings served only as corroboratory findings in the management and interpretation of results with the use of teropterin.

The predominating symptoms in our series were pain associated with malaise and local symptomatology referable to the disturbed physiology of the part affected. There was the usual history of loss of weight and strength, but for the most part the patients applied for hospitalization because of pain and inability to maintain certain body functions.

DRUG ADMINISTRATION. After a preliminary work-up, consisting of x-ray studies, blood chemistry, and hematology, the patients at the start were placed on teropterin 50 mg. daily, single, intramuscular dose, on the recommendation of Drs. SubbaRow and Farber.[5] At present, we are using 10 mg. twice daily. In one case, where a 10 mg. dose was inadvertently omitted, the patient complained of distress, and when this omission was corrected his complaint disappeared. We have noted no significant difference when teropterin was given in single or divided doses. When a patient missed medication for one or two days, we found an accentuated response to the drug upon re-institution of treatment. We are now making further studies along this line.

It was found that there was no particular advantage to be gained by intravenous administration which would outweigh the disadvantages of such a route.

As mentioned above, none of the patients was given any other form of cancer therapy. The patients were not informed that they were receiving anything special or new. This was considered important, since we wished to eliminate or at least minimize the psychogenic factor. To them, it was another among many "needles," and we can safely deny the psychogenic element at the start of the study. It was not long, however, perhaps because of the regularity of the injections or the response to them, that the patients became aware of the therapy. In cases where treatment lasted many weeks, we recognize the possibility of superimposition of psychogenic enthusiasm.

What, then, has been the response to this therapy? Almost without exception—and this includes patients who were practically moribund—the reaction has been a feeling of well-being characterized by most in the expression, "I feel like a new person." There has been a sharpening of the sensorium with a new-found interest in surroundings, and a desire for ambulation as compared to a previous state of apathy and listlessness. One patient, when asked how he felt, replied that he felt so improved that he expected to go home shortly. He died nine hours later. This feeling of being well usually became evident within a few weeks after treatment had begun, but, in some cases, strangely enough, the favorable reaction came on as early as after the third injection. We have all seen the post-transfusion response in patients where they admit to a feeling of well-being and contentment, but the response after teropterin therapy transcends that feeling and can, perhaps, best be described as "cheerfulness."

Along with this tonic response, there came, in many cases, a reduction in the amount of opiates needed for control of pain, as noted in TABLE 2. Abstracts from a few case histories may bring this more sharply into focus:

H.A., age 47, was admitted July 18, 1947. He had a reticulum cell sarcoma. We started treatment on him on August 18, 1947, and he became pain-free in ten days. He was able to get out of bed seventeen days after the institution of treatment and remained pain-free for fifty-one days until his death on October 17, 1947.

W.C., age 61, was admitted July 14, 1947. He had a malignant melanoma of the rectum. We started treatment on him on August 14, 1947, and he became pain-free in seventeen days.

E.H., age 46, was admitted September 5, 1947. She had a carcinoma of the colon with metastases with complaints of abdominal pain, anorexia, and dyspnea. We started treatment on September 22, 1947, and thirteen days later the patient stated that she had been able to have her first good meal in a month. She was happier, more communicative, and ambulant. There was no need for sedation after

TABLE 2

SHOWING REDUCTION IN THE AMOUNT OF NARCOTICS USED OR NEEDED IN A SAMPLING OF CASES

Patient	Before therapy			After therapy		
M.S.	Demerol Morphine sulfate Codeine	200 mg. 1.5 g. 10 g.	31 days	Demerol Morphine sulfate Codeine	0 0 3 g.	107 days
E.H.	Demerol Morphine sulfate Codeine	975 mg. 0 2 g.	25 days	Demerol Morphine sulfate Codeine	100 mg. 0 0	44 days
L.J.	Demerol Morphine sulfate Codeine	300 mg. 0 ½ g.	4 days	Demerol Morphine sulfate Codeine	250 mg. 0 0	64 days
S.F.	Demerol Morphine sulfate Codeine	200 mg. ½ g. 1 g.	17 days	Demerol Morphine sulfate Codeine	0 0 0	69 days
A.H.	Demerol Morphine sulfate Codeine	2400 mg. 0 0	30 days	Demerol Morphine sulfate Codeine	1700 mg. 0 0	60 days

October 18, that is, twenty-six days after the institution of treatment. She took a sudden change for the worse on November 3 and died on November 6, 1947.

C.B., age 47, was admitted on August 14, 1947. He had a carcinoma of the prostate and complained of pain in his right leg and sacrum and burning on urination. We started treatment on August 27, and he became pain-free almost immediately.

R.P., age 46, was admitted on August 15, 1947. He had a carcinoma of the stomach with extensive metastases. We started treatment on October 27, 1947, and he became pain-free after the second dose, stating that he had had his most comfortable night in weeks. His condition, however, remained poor and he died on November 26, 1947.

In this series, there were five deaths; all died pain-free without need for narcotics. They remained clear in mind until death came. In two or three cases, we noticed spiking of the temperature curve prior to exitus. The low grade spiking as a possible expression of lysis with absorption is under study at present. One incidental finding was a flattening of the pulse curve after a week or two of treatment.

In some cases, there was a rather dramatic response to the therapy. The following two cases are illustrative:

B.H., aged 65, presented an inoperable carcinoma of the esophagus. He had been treated elsewhere by radiation therapy and the implantation of radon seeds, which was followed by stricture of the esophagus, necessitating repeated dilatation. He had been unable to swallow anything but liquids for a number of months. Teropterin therapy, 50 mg. by single intramuscular injections, was given daily. After the third injection, the patient began to eat oatmeal and small meat portions. After the fifth injection, he ate a chicken dinner. Within ten days after treatment had been instituted, it was noted that his blood pressure dropped from 220/100 to 196/90, and the patient had gained six pounds. There was no appreciable change in the following two weeks, but at that time the patient reported an episode of profuse blood-tinged expectoration. The chest was examined and found to be negative. At this time, also, he described a tightening in his throat and was unable to eat solids for a period of one week. In the fourth week of treatment, the patient again improved and was able to eat solid food satisfactorily. Fluoroscopy at that time showed a change from the original string-like passage of barium to a pencil-like passage. After five weeks, the patient's blood pressure was 174/88. At present, he is maintaining his weight and working eight hours daily.

E.G., aged 65, was admitted on October 25, 1946, with inoperable carcinoma of the prostate. He had extensive metastatic lesions of the skeleton with spinal cord involvement. Clinically, he presented evidence of almost complete paresis of the lower extremities with anesthesia of the lower right extremity and partial anesthesia of the lower left extremity. There were lancinating pains associated with spasticity of the lower limbs. The legs were edematous and showed secondary joint changes. In December of 1946, an orchidectomy was performed. In early 1947, the patient received radiation therapy for a period of about three months. His response to this form of therapy was only moderate, and, because of the continued spasticity of his legs, he was given a short course of curare. Following this, physiotherapy was administered for two months. From the date of admission until teropterin therapy was instituted on October 13, 1947, the patient was largely bed-ridden, despite orchidectomy and all other forms of therapy. Three weeks after teropterin was started, he felt sensation returning to his legs and an increased ability to move them. At present, he is able to spend most of his time in a wheel chair and in a walker. One week ago, he walked un-

supported for a distance of fifteen feet. He is improving daily, and is completely pain-free. A neurological examination was made on December 2, 1947. The examiner found, "Patient is devoid of anxiety and is hopefully looking forward to his eventual recovery. The comparative examination is as follows: On October 26, 1946, he had spasms of thigh muscles, more marked on the left. Today, none is present. The marked paresis of the lower extremities has been replaced by good function. The patient is able to flex, extend, and to bicycle ride while lying on his back. He walks with a somewhat spastic gait while holding on to the bed. He is a little unsteady when walking without support, but much is due to fear and to long disuse of the balancing mechanisms. The sensory picture has returned to normal, there being no dysaesthesias and no sensory level. Reflexes of the knees are hyperactive and the ankle jerks are a little hypoactive.

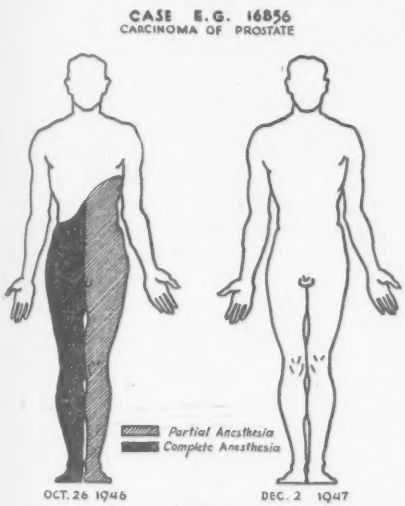

FIGURE 3.

Opinion. This patient's improvement is phenomenal, and he should be able to walk up and down stairs within the next three weeks. Nutrition has markedly improved—any further weight gain would put him into the class of early obese." (See FIGURE 3.)

Summary

Twenty of thirty-three teropterin-treated cases of malignancy are reported. These patients have been under exclusive teropterin therapy for a period of one to three months.

Laboratory studies showed that alkaline and acid phosphatase values, when abnormally high, showed a tendency to decrease following teropterin therapy. The red blood cell count and hemoglobin values were essentially unaffected.

Our clinical observations indicate that the drug is non-toxic in the dosage given. Pain was relieved in most cases, if not all, by the use of teropterin. This obviated, in the main, the necessity for further use of opiates with its concomitant depressive effects. All patients exhibited a sense of well-being, cheerfulness, and a state of mental alertness previously unseen by us in advanced malignancy. Fifteen of these twenty cases are still alive and under treatment.

Although this group of cases is too small for definite conclusions, it is our impression that teropterin therapy is a valuable adjunct in the management of malignancy, and further clinical investigation is warranted.

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THE CHEMISTRY OF CERTAIN PTEROYLGLUTAMIC ACID ANTAGONISTS

By JAMES M. SMITH, JR., DONNA B. COSULICH, MARTIN E. HULTQUIST, AND DORIS R. SEEGER*

Chemical analogues which are metabolite antagonists are known for a large number of essential metabolites, including all the known members of the vitamin B complex. Analogues of pteroylglutamic acid (I) have been studied extensively by the Research Groups at the Lederle Laboratories Division and the Calco Chemical Division, American Cyanamid Company.

The analogues to be discussed in this paper are of three main types: First, the analogue in which the glutamic acid is replaced by another amino acid, the remainder of the molecule being unchanged; second, an analogue in which the substituents on the pteridine ring are different; third, an analogue in which a substituent is introduced on the amino group of the *p*-aminobenzoylglutamic acid part of the molecule; and, finally, an example of a combination of two variations. All of these analogues have been isolated in pure form.

The method of synthesis is the Waller reaction[1] in which 2,4,5-triamino-6-hydroxypyrimidine, 2,3-dibromopropionaldehyde, and *p*-aminobenzoylglutamic acid are mixed in water at pH 3-4.

This is a general reaction for the synthesis of pteroylglutamic acid analogues. Other *p*-aminobenzoylamino acids may be substituted for *p*-aminobenzoylglutamic acid, as, for example, *p*-aminobenzoylaspartic acid. Other 4,5-diaminopyrimidines may be substituted for 2,4,5-triamino-6-hydroxypyrimidine, as, for example, 2,4,5,6-tetraminopyrimidine. For *p*-aminobenzoylglutamic acid, *p*-(N-methylamino)benzoylglutamic acid may be substituted, which gives a methylpteroylglutamic acid.

Pteroylaspartic acid (II) was prepared by the above method soon after the structure of pteroylglutamic acid had been elucidated, and the preparation and properties of this compound have been described in detail by Hutchings *et al.*[2] It is an antagonist for pteroylglutamic acid in the growth of *Streptococcus faecalis* R.

The analogue having an amino group instead of the hydroxyl in the 4-position, N-[4-{[(2,4-diamino-6-pteridyl)-methyl]amino}benzoyl]glutamic acid (III), has been reported by Seeger, Smith, and Hultquist.[3] It was synthesized by the Waller reaction as described above and purified by a process very similar to that for pteroylglutamic acid.[1] It was isolated both as the free acid and as the magnesium salt. The 4-amino derivative is considerably more soluble than pteroylglutamic acid. The structure was assigned by comparison of the ultraviolet absorption data with that for pteroylglutamic acid and by degradation studies similar to those used for structure proof of the latter. There is little doubt that the structure is as given, with the side chain in the 6- position on the pteridine ring and amino groups in the 2- and 4- positions. The details of this work will be published elsewhere.

The 4-amino derivatives are powerful antagonists for pteroylglutamic acid in the growth of *Streptococcus faecalis* R. A number of 2,4-diamino-6,7- disubstituted pteridines which also have antagonist activity have been reported by Cain, Mallette, and Taylor.[4]

A methyl group was introduced into the pteroylglutamic acid molecule by using *p*-(N-methylamino)benzoylglutamic acid in place of *p*-aminobenzoylglutamic acid in the reaction described before.

The product, N-[4-{N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-N-methylamino}benzoyl]glutamic acid (IV),[5] was purified by a method similar to that described previously. The pteroic acid analogue, 4-{N-[(2-amino-4-hydroxy-6-pteridyl)methyl]-N-methylamino}benzoic acid (V),[5] was also prepared in a similar reaction using *p*-(N-methylamino) benzoic acid.

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The structures are assigned from ultraviolet absorption data and degradation studies. These analogues are antagonists.

A recent publication, by Wolf *et al.*,[6] describes the structure of rhizopterin, formerly known as the "S.L.R. factor," as *p*-[N-(2-amino-4-hydroxypyrimido[4,5-b] pyrazin-6-ylmethyl)-formamido]-benzoic acid. It is interesting that this compound, which has a formyl group in the same position as the methyl group in our compound (V), is a growth factor rather than an antagonist for the growth of *Streptococcus faecalis* R.

Examples of a combination of these variations in the structure of pteroylglutamic acid are N-[4-{ N-[(2,4-diamino-6-pteridyl) methyl]-N-methylamino } benzoyl] glutamic acid (VI) and 4-{ N-[(2,4-diamino-6-pteridyl) methyl]-N-methylamino } benzoic acid (VII). This type has an amino group in the 4- position as well as a methyl group on the *p*-amino nitrogen of *p*-aminobenzoylglutamic acid.

A number of other variations and combinations thereof have been made in the pteroylglutamic acid molecule. A detailed discussion of these compounds is beyond the scope of this paper, but reports will appear in the literature subsequently.

The biological activity of these compounds has been examined by Drs. B. L. Hutchings and E. L. R. Stokstad of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y. A comparison of the antagonist activity of a series of analogues is given in TABLE 1.

TABLE 1

RELATIVE ACTIVITY OF PTEROYLGLUTAMIC ACID ANTAGONISTS (PURIFIED)

Compound No.	Antagonist activity (*Streptococcus faecalis* R)
III	700
IV	100
V	15
VI	800
VII	162

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THE ROUS CHICKEN SARCOMA IN BIRDS TREATED WITH FOLIC ACID AND ITS DERIVATIVES: A PATHOLOGICAL STUDY

By EPHRAIM WOLL*

The purpose of the present study was (1) to evaluate the natural history of the tumor in the untreated bird; (2) to define the natural variations of its course, gross and microscopic features; and (3) to compare these with the findings in birds treated with folic acid, its derivatives, and in birds maintained on a folic acid deficient diet.

REVIEW OF LITERATURE

The subject of filterable tumors in fowl was reviewed by Gye and Purdy in 1931,[1] and by Foulds in 1934.[2] The preceding studies were concerned mainly with the problems of etiology, transmission, and immunology. Morphology of the tumor was studied among others by Rous,[3, 4, 5] Peyron,[6] Roskin,[7] Fujinami,[8] and Foulds.[9]

From the time of its discovery in 1910, when transmission was at best difficult, and possible only to birds actually related to the original animal, successive tumor generations have now reached a state of great virulence. The tumor is now readily passed to other breeds of chickens. In our hands, it has been 84.4 per cent successful in 5-7 week-old chickens and 100 per cent successful in baby chicks. The latter finding is in accord with that of Sugiura.[10]

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The original tumor, as described by Rous,[3] was a well-defined, firm, opaque mass which shelled out readily. In the center coagulation, necrosis was marked. The rim was composed of friable, yellowish-pink, finely striated tissue. The typical microscopical pattern was that of loose bundles of spindle cells with vesicular nuclei and intercellular fibrils. Small round cells with a myxomatous intercellular substance were also seen at the advancing edges of the growth. The actively growing tumor is now much more infiltrative, especially in the baby chick. Hemorrhage, infarction, liquefaction, and myxomatous degeneration are prominent features. The typical cell is more likely to be small, round, growing in irregular masses, with scant stroma.

Careful studies were made, by Rous and Murphy, of the histology of the tumor in resistant animals.[4] The characteristic findings were: (1) Large local and diffuse collections of lymphocytes. These were first seen near the vessels and periphery of the tumor. (2) Attenuation of the spindle shape. (3) Hydropic degeneration of the cytoplasm. (4) Presence of multinucleated giant cells. (5) Profuse ingrowth of capillaries and fibroblasts. (6) Ultimate disappearance of the tumor with or without residual scarring. Rous and Murphy found that in the first 2 days after grafting the tumor cells proliferate actively in the susceptible as well as the resistant host. The subsequent days are marked by either continued growth or retrogression.

MATERIALS AND METHODS

The conclusions of this paper are based on gross and microscopic examination of approximately 350 birds ranging in age from 2 days to 10 weeks. The source of the inoculum, method and site of introduction, and other related information are described by Little *et al.* in the following paper.[11] The breeds included New Hampshire Red and a small number of Plymouth Rock. In almost all instances, the animals were killed with chloroform or other suitable methods, and autopsied within one hour of death. Representative blocks of the tumor were fixed in Zenker-formol solution. A large number were fixed in neutral formaldehyde and Zenker-acetic acid. The sections were stained with hematoxylin and eosin, and a small number with eosin-methylene blue, phloxine-methylene blue, and Shorr's modification of Masson's trichrome stain. A few sections were fixed and stained for glycogen and mucin. In all cases, the viscera were inspected and all gross evidence of metastasis or any other departure from the normal was noted. While numerous blocks of tissue from the viscera were taken, no exhaustive study of the normal or abnormal findings in the treated or control animals was made. This phase of the problem is being investigated now.

The gross and microscopic findings were tabulated in terms of criteria to be described below. In the interest of objectivity, many of the gross and all of the microscopic examinations were made without previous knowledge of the treatment used.

RESULTS AND ANALYSIS

PATHOLOGY OF THE UNTREATED BIRDS—*General Considerations.* Most of the past study of this tumor was expressed in static terms. It was described as it appeared at any given time, without consideration of the antecedents and consequents. In the original studies of Rous and Murphy, the tumor was described dynamically, in its natural history as well as in relation to the host.[4, 5] Just as there are slowly and rapidly growing variants of the same tumor, there are corresponding morphological differences between the two. Surely these differences are not absolute. Individual elements characteristic of relative benignancy or malignancy are seen in a given tumor, but the overall summation permits judgment at least of the two extremes of this range.

TABLE 1

GROSS FINDINGS

	Rapid	Slow
Skin	Discolored, blue-green	Clear
Subcutaneous space	Edematous, massive hemorrhage, occasional tumor extensions	Clear
Tumor consistency	Soft, occasionally fluctuant	Firm to hard, occasionally nodular
Size	Large, limited by anatomical boundaries	Small, occasionally minimal, discrete
Margins	Vague	Sharp
Cross section		
Color	Light grey, translucent, mottled	Pale yellow, opaque, homogeneous
Rim	Translucent, occasionally opaque	Opaque
Center	Liquefied, viscid, hemorrhagic, occasionally cystic	Firm, homogeneous, occasionally small central areas of myxomatous liquefaction
Lobulations	Absent	Often present
Hemorrhage	Severe, early, massive	Slight to moderate early
Infarction	Massive	Absent or minimal
Myxomatous change	Marked or absent	Absent

TABLE 2

MICROSCOPIC FINDINGS

	Rapid	Slow
Type cell	Small, round or spindle, in fascicles, occasionally irregular masses	Giant round, or fibroblast in thick fascicles
Cytoplasm	Light purple, homogeneous	Pink, granular, vacuolated
Mitoses	2-3, occasionally 4-5	Rare
Vascularity	Sinusoidal	"Granulomatous"
Stroma	Scant	Abundant
Lymphocytes	Few	Numerous
Polymorphs	Very numerous	Numerous
Macrophages	Few	Many
Giant cells	Absent or rare	Numerous
Fibroblasts	Rare	Most common cell
Collagen	Very scant	Scant
Invasion	Rapid, active	Slow or absent
Metastases	Common	Extremely rare

Criteria. TABLES 1 and 2 summarize the gross and microscopic differences between the slowly and rapidly growing tumors.

External examination. The earliest naked-eye evidence of tumor growth is noted 3 days after intramuscular inoculation. In 10 to 20 days, a small nodule can be felt in the muscle at the site of injection. In the untreated animal, the tumor grows rapidly and steadily until the whole side of the thorax bulges forward yet retains a normal contour. Maximal growth is reached in the next 7-10 days, at which point the animal usually dies. The largest growth is, apparently, only limited by the anatomical boundaries of the fascia, muscle bundles, etc. In no case was the tumor seen to extend across the mid-line. On palpation, the tumor is often fluctuant. The overlying skin is freely mobile, markedly discolored a deep blue or green. Occasionally, a separate discrete tumor mass is felt in the subcutaneous space or corium.

This is apparently a growth related to the needle track of the inoculation.

Subcutaneous Space. The blue discoloration is apparently related to the hemorrhage. It is to be noted that even in the most severe old hemorrhage the amount of hemosiderin is small.

Necrosis. The amount of liquefaction, hemorrhage, and necrosis may be particularly large so that the tumor is transformed into a cystic cavity lined with a relatively thin layer of viable tissue. It is of interest to note that small nodular masses of young tumor cells, as judged by the above criteria, can be seen growing on the inner lining of such cavities. It would seem, therefore, that the liquefied material, if not favorable, is at least not an inhibitory *milieu* for growth. Something akin to this is seen in the presence of intra-abdominal masses of tumor where viable, actively growing cells are seen in the midst of mucinous and hemorrhagic fluid. Rous[5] comments on the "culture" appearance of tumor growing on the surface of the liver without any vascular connection with the latter. Similar growths were observed in chick embryos.

Lobulations. These, on microscopic examination, are bands of connective tissue with accompanying capillaries entering the tumor from the adjacent musculature.

Hemorrhage. This is most prominent in the full-blown type, yet hemorrhage is a frequent accompaniment of early rapid growth. It was seen 3 days after inoculation. Several observers speak of a hemorrhagic disease in chicks in association with the sarcoma. In our experience, hemorrhage was invariably associated with tumor growth and not evident independently.

Mucin. It is not clear whether this substance, staining purple with hematoxylin and deep blue with Myer's muchematein stain, is a product of degeneration due to ischemia or a substance elaborated by viable, actively proliferating, undifferentiated cells. It is seen in both cases, more commonly in the former.

Type Cell. The least differentiated variant is a small round cell with a vesicular nucleus, prominent compact nucleolus, scant, very finely granular purple cytoplasm, and poorly defined cell margin. These cells lack any specific configuration. At times, they line the sarcolemma lining of a space formerly occupied by a muscle fiber. A more differentiated variant is a small spindle cell with essentially similar features as above plus delicate cytoplasmic processes in the long axis, resembling the mesenchymal fibroblasts. The retrogressing tumor shows numerous swollen spindle or round cells with a clear peripheral zone of cytoplasm. Occasionally, these are multinucleated. Careful search for intracellular fibrils does not show these to be present in any of the tumor cells, nor is there any stainable glycogen.

Mitosis. This is not a prominent feature of the tumor. The frequency is from an occasional mitotic figure in many fields in the slow tumor to 4 or 5 per high-power field in the rapidly growing type. Mitotic figures are particularly common in the tumors of baby chicks. They are apparently normal. In giant tumor cells, the chromosomes occasionally appear fragmented and are arranged radially. In only one instance was a triaster seen; this isolated observation is therefore unreliable. Grading of the tumor on the basis of mitotic activity is useful only at the two extremes, namely, the slow and rapidly growing tumors.

Captions for FIGURES 1-6 (*see opposite page*).

FIGURE 1. Tumor 3 days after inoculation. Note the grey translucent nodules with surrounding hyperemia (untreated).

FIGURE 2. External view of tumor inoculated in the neck (untreated).

FIGURE 3. Slowly growing tumor in naturally resistant 5-week-old chicken. Note the light yellow, opaque, confluent, nodular masses (untreated).

FIGURE 4. Cross-section view of tumor in baby chick treated with folic acid-free diet and folic acid supplement.

FIGURE 5. External view of tumor in a bird treated with 4-amino-folic/d(-) glutamic acid. Note the small size and discrete character of growth.

FIGURE 6. Cross section view of tumor in FIGURE 5.

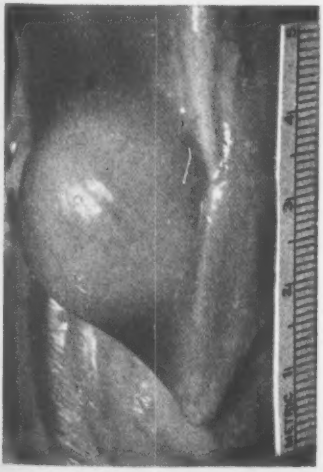
1

2

3

4

5



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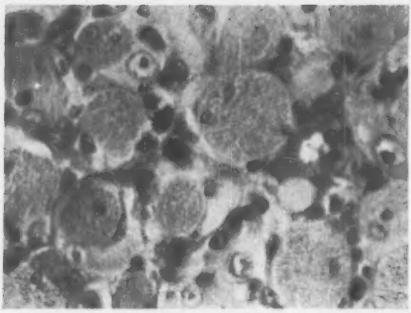

FIGURE 7. Early growth. Note the displacement and compression of the muscle fibers. Shorr's modification of Masson's trichrome stain, X300.

FIGURE 10. Spindle cells of a rapidly growing tumor. Shorr's modification of Masson's trichrome stain, X300.

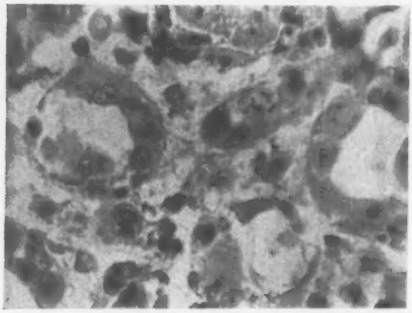

FIGURE 8. A somewhat later growth than in FIGURE 7. Note the arrangement of the tumor cells along the sarcolemma and the myxomatous change. Hematoxylin-eosin, X300.

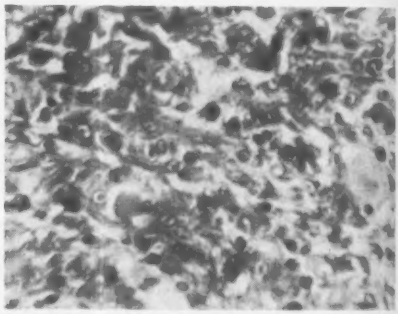

FIGURE 11. Tumor in a naturally resistant animal. Note the abundance of fibroblasts, lymphocytes, and collagen. Hematoxylin-eosin, X270.

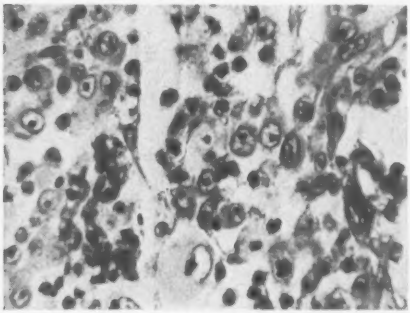

FIGURE 9. Undifferentiated cells of a rapidly growing tumor. One degenerating cell is also shown. Hematoxylin-eosin, X270.

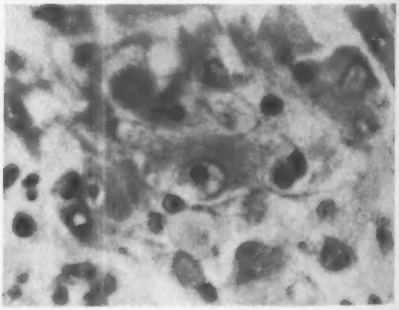

FIGURE 12. Hydropic degeneration and swelling of tumor cells. Note the vacuoles in the nucleus and cytoplasm.

Stroma. This forms the most prominent feature of the slowly growing variant. It is difficult to decide whether the fibroblasts are differentiated tumor cells, proliferations from adjacent normal tissue, or a mixture of both. The association of capillaries and collagen inclines one to the last two possibilities.

Invasion. In general, the tumor is of low invasiveness except in the baby chick.

It usually insinuates itself between muscle fibers or other anatomical barriers. In a rapid advance, a good deal of degenerating muscle is seen in the depths of the tumor. On gross examination, the opaque yellow rim of an otherwise apparently rapidly growing type should not be misinterpreted for a wall of effective tissue reaction but rather is a massive compression and degeneration of adjacent musculature.

Metastases. In contrast with previous observations, the incidence of metastases in our series was not more than 15 to 20 per cent. These were seen most commonly in the lungs and less so in the liver. In all instances but one, the metastases were associated with rapid growth. It is of interest to note that the dermis and subcutaneous space of the chicken has numerous vascular plexuses of considerable size. Thus, subcutaneous or intradermal inoculation may result in more frequent metastasis. Nevertheless, in our experience, the incidence of distant spread in intramuscular inoculation was still less than in previous reports.

Histogenesis. The histogenesis of the tumor is still not a settled problem. It is held by most that it is a connective tissue sarcoma. Carrel's[12, 13] and Roskin's[7] studies suggest that it is related to the reticulo-endothelial system. The evidence of phagocytosis by tumor cells supports this. The resemblance to human rhabdomyosarcoma or myoblastoma is striking except for the absence of any cross-striations or centrioles. The nature of the sarcolemma is still not settled by histologists. Possibly, the elucidation of this problem may throw light on the tissue origin of the Rous sarcoma.

PATHOLOGY OF THE TREATED BIRDS—*General Considerations.* The experiments described by Little *et al.*[11] should be viewed in the light of the following observations: (1) The effectiveness of the chemicals used to inhibit tumor growth is contingent with its continued administration. In some of the experiments, the birds were examined after a prolonged period during which treatment was discontinued. There was recrudescence of growth with a final poor result. (2) Delayed treatment, until a tumor is well developed, is ineffective or slightly so. (3) Highly effective tumor inhibitors were associated with toxic effects characterized by malnutrition, underdevelopment, or outright lethal action (amino folic acid in baby chicks). No specific morphological changes attributable to this toxic action were found in the viscera. The effect on the hematopoietic and central nervous systems is being explored now. (4) In many instances, notably in the case of baby chicks placed on a folic acid deficient diet, there were no traces of tumor or even of a residual inflammatory reaction at the site of inoculation. We believe that this complete, albeit temporary, inhibition is valid because of the great susceptibility of baby chicks to the tumor. (5) The animals in this study represent but a sample of a considerably larger number observed. The findings in the whole group and those of the pathological study are substantially in accord. (6) Except for the baby chicks on a folic acid deficient diet, where tumor inhibition was complete for the period of observation, and for baby chicks on the same diet with folic acid supplement, where all animals showed early and maximal tumor growth, the effectiveness of a given chemical was not uniform. In each experiment, there were examples that did not conform to the general pattern of the group. Factors which may account for this variation are: (a) dosage, (b) delay in treatment after inoculation, (c) discontinuance of treatment, (d) toxic effects, (e) age of animals, (f) natural resistance, and (g) technical difficulties. There are, undoubtedly, other factors at present unknown to us. With baby chicks of definitely known age and lineage, the results were much more clear-cut and uniform.

The chief manifestations of effective treatments were: (1) Complete absence of tumor. The time of observation was

usually over 20 days, a period beyond the expected in which the animals should have well-developed tumors or even be dead as result. This was especially true of baby chicks. (2) Fewer and slower growing tumors. These were similar, grossly and microscopically, to the tumors of naturally resistant animals, but with the following differences. The extent of hydropic degeneration was considerably greater without corresponding organization and differentiation. Lymphocyte response was not as pronounced. This degeneration was seen at the periphery as well as in the center and, therefore, apparently had no relation to ischemia. (3) The almost complete lack of metastases. This must be qualified by the observation that, in baby chicks, direct tumor extension into the subjacent liver was rather common. We believe this to be due to the more infiltrative character of the tumor in the young, or to technical difficulties of injection in a small animal, or both.

Discussion. Most of the above observations of the untreated bird are not original contributions to the pathology of Rous sarcoma. They have been made before by various observers, although often incompletely or in static terms. We feel justified in presenting them here because they represent the yardstick by which effectiveness of treatment in terms of pathology was measured.

Hemorrhage, infarction, and ischemia, with associated cellular death, degeneration, and inflammatory response are prominent features of rapid growth. Of these, central ischemia is the most constant. In contrast, slow growth in the resistant animal is characterized mainly by reduced cellular division, mitotic or amitotic; differentiation of the tumor cells into mature fibrocytes with collagen; and cellular degeneration and organization-repair with or without scarring.

The whole range of individual gross and microscopic appearances was seen in both the treated and untreated birds. Careful comparisons were made and no distinctive pattern or cytological detail could be found which was specific to either of the two groups. Yet, there is the impression that the inhibited tumor in the treated series shows much more cytological degeneration and, possibly, disruption of its mitotic figures. This raises the question—Is effective treatment an interference with the metabolism of the tumor cell? This problem is being explored further.

Our study emphasizes one factor in the biology of tumors, namely, the nutritional status of the host. The use of folic acid, its derivatives and antagonists, offers a valuable tool in the study of this problem.

SUMMARY AND CONCLUSIONS

(1) Approximately 350 birds, part of a considerably larger observed group, were inoculated with Rous chicken sarcoma, treated with folic acid, its derivatives, or a folic acid free diet.

(2) The morphologic features of the tumor in its life history and natural variations in the untreated bird are described and compared with those of treated animals.

(3) Certain of the folic acid derivatives completely or partly inhibit tumor growth, but may be associated with toxic effects.

(4) A folic acid free diet protects baby chicks against the tumor.

(5) The above actions are contingent on early and continued treatment.

(6) The addition of folic acid to a folic acid free diet materially increases the incidence and apparently enhances the growth of the tumor.

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THE EFFECT OF FOLIC ACID AND ITS ANTAGONISTS ON ROUS CHICKEN SARCOMA

By PAUL A. LITTLE, ANGUS SAMPATH, V. PAGANELLI, E. LOCKE, AND Y. SUBBAROW *

Introduction. Rous chicken sarcoma is a virus disease which has been extensively investigated since its discovery by Rous (1910). Peacock (1946) has recently evaluated the various findings concerning virus-induced fowl sarcomas and the chemically induced fowl sarcomas and has concluded that there is no reason to postulate a common etiology. Dr. Woll, in the preceding paper, has studied the pathology of the virus-induced sarcoma which is the subject of this report and has presented his findings.

In our laboratory, the growth of chicken tumors induced by virus inoculation has been completely prevented by maintaining the birds on a synthetic, folic acid free diet. Baby chicks were found to be more satisfactory for this demonstration than six weeks old birds in that the tumors were prevented in only forty per cent of the older birds and in a hundred per cent of baby chicks. We have also been able to prevent the growth of chicken tumors by use of chemical antagonists of folic acid.

Our exploratory studies consisted of experiments with four to nine weeks old New Hampshire Red chickens. A most valuable result of these experiments was the collection of data showing the uniformly high susceptibility of the birds used. The birds were treated from the time of first appearance of breast nodules until it was found that the number of naturally resistant birds encountered had not been more than ten per cent. Over three hundred birds were used. This high degree of success in inducing chicken tumors by virus inoculation may possibly be due to our choice of birds.

Selection of Chickens. In planning this work, we selected a single flock from several flocks of the New Hampshire Red variety that are maintained by Mr. Peter Pulis at Spring Lake Farm, Wyckoff, New Jersey. We had previously found that two of these flocks regularly produced chicks which were resistant to inoculation with Newcastle virus to the extent of 25 to 50 per cent even though there had been no history of the disease in them. We had found that two other flocks regularly produced chicks which were susceptible to inoculation with Newcastle virus to the extent of 90 to 100 per cent. A Newcastle virus susceptible flock was selected as the source of all of the birds used in our studies of chicken tumor. The four to nine weeks old birds were raised for us in flocks of three hundred and supplied in groups of fifty. The baby chicks were delivered to us when one day old. As many as two hundred baby chicks were employed in a single test. Day-old chicks were used for studies of the effect of chemical with synthetic diet. Five to six day old chicks

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were used for studies of the more toxic folic acid antagonists with ordinary diet.

Method of Inoculation. The virus used in our experiments was prepared from selected breast tumors produced by inoculating four to nine weeks old birds in the pectoral muscle with one milliliter amounts of Rous sarcoma virus. The virus was originally obtained from Dr. James B. Murphy of the Rockefeller Institute. Birds having firm, well-developed tumors were sacrificed and the infected tissues were removed, cut into cubic centimeter pieces, placed in sterile vials, and stored in a dry-ice chest until used. The suspensions of virus used for inoculation consisted of the tissue from one vial dispersed with the aid of a Ten Broeck grinder in 100 milliliters of cold, sterile, distilled water. Inoculations were made within an hour from the time that the suspensions were prepared.

Since baby chicks were used in collecting most of the data presented at this time, their method of inoculation will be described in detail. The chicks were injected in the right breast with 0.2 milliliter of standardized suspension of tumor tissue after removing the feathers from the breast area. The injection was subcutaneous and inflated the skin over the whole area of the right breast until the material was absorbed. The point of entry used in making the injection was standardized and was located within 0.3 centimeter of and at half the length of the sternum. Groups of ten chicks were used for each determination and for untreated controls. Groups were treated by daily intraperitoneal injections of chemical starting on the day on which the virus was inoculated.

Special Conditions for Various Purposes. In our experiments, we have employed special conditions for various purposes. As previously stated, we treated four to nine weeks old birds from the time of first appearance of breast nodules for the purpose of eliminating naturally resistant birds. When it was found that we could depend on the high susceptibility of the birds used, we treated the birds from the time of inoculation of virus. Our first demonstration of the inhibitory effect of synthetic, folic acid free diet was made with six weeks old birds, which were fed the diet from the time of inoculation of virus. A group of ten birds which received the diet alone was resistant to inoculation to the extent of forty per cent, whereas another group of ten which received 0.1 milligram per cent of folic acid in the diet was resistant to the extent of only ten per cent. Baby chicks were found to be more satisfactory for this demonstration, possibly because they have a less highly developed microbial flora of crop and intestine. Oleson and co-workers (1946) have described the effect of the diet used by us on day-old white Leghorn chicks. For our purpose, it was not necessary to maintain the chicks on this diet for longer than three weeks.

Because of ease of handling, baby chicks were found to be useful in making quantitative studies, except in the case of a particular chemical, 4-amino-folic acid, which proved to be highly toxic. The activity of this chemical was best demonstrated by use of the older birds.

For the purpose of demonstrating the virus-stimulating effect of certain chemicals, baby chicks were maintained on synthetic, folic acid free diet and injected daily with the chemical. For the purpose of demonstrating the virus-inhibiting effects of other chemicals, baby chicks were maintained on ordinary diet which regularly permitted ninety per cent of untreated birds to develop tumors.

The Virus-Stimulating Effect of Chemicals. TABLE 1 illustrates the results of tests in which baby chicks were maintained on synthetic, folic acid free diet for the purpose of determining the virus-stimulating effect of chemicals. The method of determining and recording the different stages of development of breast tumors was based upon our knowledge of the maximum capacity of the breast. It was found that various workers could make essentially similar observations after

TABLE 1

PROTOCOL OF A BABY-CHICK TEST USING A SYNTHETIC, FOLIC ACID FREE DIET

Bird No.	Selected results from the record of daily observations				
	8th Day	10th Day	12th Day	14th Day	16th Day
Effect of synthetic, folic acid free diet alone					
2348	....	....	....	....	....
2349	....	....	....	....	....
2350	....	....	....	....	....
2351	....	....	....	....	....
2352	....	....	....	....	....
2353	....	....	....	....	....
2354	....	....	....	....	....
2355	....	....	....	....	....
2356	....	....	....	....	....
2357	....	....	....	....	....
Per cent	0	0	0	0	0
Effect of injecting 100 micrograms/day of folic acid					
2360	....	....	....	....	....
2361	?	P	2P	3P	4P
2362	....	....	....	?	P
2363	....	P	P	2P	3P
2364	....	P	2P	3P	Dead
2365	?	2P	2P	3P	4P
2366	....	P	2P	3P	4P
2367	....	P	2P	3P	4P
2368	?	2P	2P	3P	4P
2369	....	P	2P	3P	4P
Per cent	30	80	80	90	90

P: palpable swelling.
2P: ¼ to ½ full size.
3P: ½ to ⅞ full size.
4P: full size.

TABLE 2

RESULTS OF BABY-CHICK TESTS USING A SYNTHETIC, FOLIC ACID FREE DIET

Chemical injected	Micrograms per day	Total chicks	Per cent chicks with tumor
None (four tests)	...	40	0
Folic acid	500	10	80
	100	10	90
	10	10	60
Folic acid with d(—) glutamic acid	100	10	0
	10	10	0
N-methyl-folic acid	100	10	80
Pteroyldiglutamic acid	500	10	90
Pteroyltriglutamic acid	500	10	100
Pteroylaspartic acid	100	10	0
Pteroic acid	100	10	0
N-methylpteroic acid	100	10	0
P.A.B.-triglutamic acid	100	10	0

a preliminary inspection of a series of tumors in different stages of development.

The earliest evidence of tumor usually consisted of a slight elevation of the lower margin of the breast. This symptom was noted, in the record of results, as "questionable." Thereafter, almost daily changes occurred and were recorded in the following manner:

Symbol	*Meaning*
P	Palpable swelling
2P	Tumor ¼ to ½ full size
3P	Tumor ½ to ⅔ full size
4P	Tumor full size

Observations were made daily, beginning with the eighth day and continuing until the differences had been clearly demonstrated, at which time the birds were sacrificed and examined for internal evidence of tumor. The pathological studies were made by Dr. E. Woll.

As demonstrated in TABLE 1, the synthetic, folic acid free diet completely prevented the occurrence of breast tumors in the baby chicks, but nearly all of the chicks developed tumor when injected daily with folic acid. This result was regularly confirmed in the different tests in which we studied the virus-stimulating effect of other chemicals.

TABLE 2 shows the result of giving baby chicks, maintained on synthetic, folic acid free diet, daily injections of chemicals which are closely related to folic acid. It will be noted that folic acid with d(—) glutamic acid had no virus-stimulating effect. L(+) glutamic acid is the naturally occurring form found in the body and in the vitamin. N-methyl-folic acid, pteroyldiglutamic acid, and pteroyltriglutamic acid all contain the natural form of glutamic acid and showed as great a virus-stimulating effect as folic acid. Pteroylaspartic acid, pteroic acid, N-methylpteroic acid, and P.A.B.-triglutamic acid had no virus-stimulating effect. Chemicals which will be dealt with subsequently as folic acid antagonists also had no virus-stimulating effect.

This part of our report would not be complete without presentation of the formula of the synthetic, folic acid free diet used. As shown in TABLE 3, this diet contained adequate amounts of the thirteen vitamins which, together with folic acid, are required for complete nutrition of the chicken. Oleson and associates (1946) have described the effect of this diet on the feathering of chickens.

TABLE 3

FORMULA OF THE SYNTHETIC, FOLIC ACID FREE DIET USED IN CHICK TESTS

(This diet was made up by Dr. J. J. Oleson of our laboratories)

Cerelose	53.0%
Alc. ext. casein	22.0%
Salt mixture	4.3%
Calcium gluconate	3.0%
Gelatin	8.0%
Ruffex	4.0%
Soybean oil	5.0%
Cholic acid	0.25%
Cystine	0.45%
Choline chloride	200 mg. %
Calcium pantothenate	3 mg. %
Nicotinic amide	3 mg. %
Pyridoxine	0.5 mg. %
Thiamin chloride	0.3 mg. %
Biotin	0.03 mg. %
Riboflavin	0.5 mg. %
Inositol	100 mg. %
P.A.B.	5 mg. %
Vitamin E	5 mg. %
Vitamin K	0.2 mg. %
Vitamin A	3,500 units %
Vitamin D	200 units %

The Virus-Inhibiting Effect of Chemicals. TABLE 4 illustrates the results of tests in which baby chicks were maintained on a diet of ordinary chick-feed for the purpose of determining the virus-inhibiting effect of chemicals. The standard brand of prepared feed contained alfalfa meal, corn gluten meal, wheat bran, distillers dried solubles, dried buttermilk, fish meal, meat scrap, ground yellow corn, bone meal, pulverized oats, wheat middlings, soy bean oil meal, ground limestone, iodized salt, fortified vitamin A and D feeding oil, vitamin D-activated animal sterol, manganese sulphate, and riboflavin supplement.

TABLE 4

PROTOCOL OF A BABY-CHICK TEST USING A DIET OF ORDINARY CHICK-FEED

Bird No.	Selected results from the record of daily observations				
	12th Day	14th Day	16th Day	18th Day	20th Day
Effect of ordinary diet alone					
1171	2P	3P	4P	4P	4P
1172	P	2P	2P	3P	3P
1173	2P	4P	4P	4P	4P
1174	P	3P	3P	4P	4P
1175	....	P	P	3P	3P
1176	P	2P	3P	4P	4P
1177	....	P	2P	3P	3P
1178	....	....	....	....	....
1179	....	P	3P	4P	4P
1180	2P	4P	4P	4P	4P
Per cent	60	90	90	90	90
Effect of injecting 400 micrograms/day of 4-amino-pteroylaspartic acid					
1240	....	....	....	....	....
1241	....	....	....	....	....
1242	....	....	....	P	P
1243	....	....	....	....	....
1244	....	....	....	....	P
1245	....	....	....	....	....
1246	....	....	....	P	2P
1247	....	....	....	....	....
1248	....	....	....	....	P
1249	....	....	....	....	....
Per cent	0	0	0	20	40

P: palpable swelling.
2P: ¼ to ½ full size.
3P: ½ to ¾ full size.
4P: full size.

TABLE 5

RESULTS OF BABY-CHICK TESTS USING A DIET OF ORDINARY CHICK-FEED

Chemical injected	Micrograms per day	Total chicks	Per cent chicks with tumor		
			12th Day	16th Day	20th Day
None (four tests)	....	40	52	87	95
4-amino-pteroylaspartic acid	400	10	0	0	40
	200	10	0	30	40
	100	10	0	30	60
	20	10	0	60	60
4-amino-folic acid with d(—) glutamic acid	400	10	0	0	0
	200	10	0	10	50
	100	10	0	30	40
	20	10	0	40	60
4-amino-N-methyl-folic acid	100	10	30	60	70
4-amino-N-methyl-pteroic acid	100	10	40	50	60
Pteroylaspartic acid	100	10	30	80	90
Folic acid with d(—) glutamic acid	400	10	70	80	90

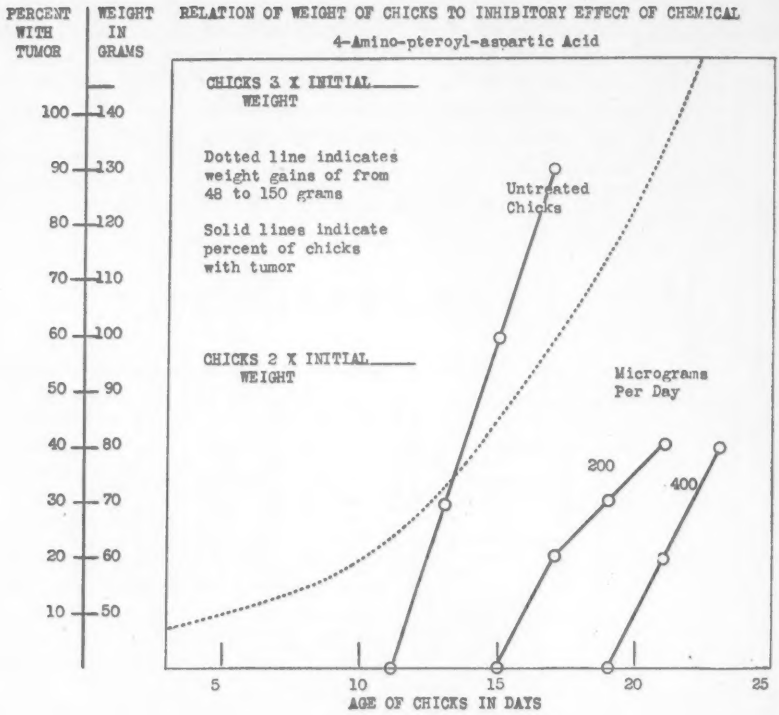

FIGURE 1.

As demonstrated in TABLE 4, nearly all of the chicks developed tumor when maintained on this diet. This result was regularly confirmed in the different tests in which we studied the virus-inhibiting effect of chemicals such as 4-amino-pteroyl-aspartic acid. The effect of injecting 400 micrograms per day of this chemical is seen to consist of a long delay in the appearance of any tumor and a marked decrease in the number of birds developing tumors.

TABLE 5 shows some of the quantitative data which we have collected on the virus-inhibiting effect of 4-amino-pteroylaspartic acid, 4-amino-folic acid with d(—) glutamic acid, and other chemicals of interest here. By comparing the percentage of birds exhibiting tumor on the 12th, 16th, and 20th day, we observe that there is a relationship between the amount of chemical injected, the time of appearance of any evidence of tumor, and the number of birds developing tumor. Doses of 100 micrograms of 4-amino-pteroylaspartic acid and 4-amino-folic acid with d(—) glutamic acid are seen to be more active than similar doses of 4-amino-N-methyl folic acid, 4-amino-N-methylpteroic acid, and pteroylaspartic acid. Doses of 400 micrograms of folic acid with d(—) glutamic acid are seen to be inactive. Sulfadiazine was also tested at doses of one milligram because of its well-known ability to antagonize a part of the folic acid molecule, and was found to be completely inactive.

The Problem of Dosage. As shown in

FIGURE 1, the inhibitory effects which we have demonstrated were undoubtedly diminished by the fact that the chicks were constantly growing. FIGURE 1 shows the daily gains in weight of the treated chicks and the results of daily injections of fixed doses of 400 and 200 micrograms of 4-amino-pteroylaspartic acid. By the 16th day, the chicks had increased to twice, and by the twenty-second day to three times their original weight. Probably the use of doses of chemicals based on milligrams per kilogram of body weight would be a more effective procedure.

The Toxicity and Virus-Inhibiting Effect of 4-Amino-Folic Acid. In its virus-inhibiting effect, another chemical, 4-amino-folic acid with 1(+) glutamic acid, was found to be even more active than either 4-amino-pteroylaspartic acid or 4-amino-folic acid with d(—) glutamic acid. Its virus-inhibiting effect was repeatedly demonstrated in our experiments with four to nine weeks old chickens, not only when treatment was started from the time of inoculation, but also when treatment was started after the sarcoma had started to grow and breast nodules had formed.

TABLE 6 shows the results of a comparative study of the activity of 4-amino-folic acid with 1(+) glutamic acid and

TABLE 6

PROTOCOL OF A TEST OF FOLIC ACID ANTAGONISTS USING SEVEN WEEKS OLD CHICKENS

Bird No.	Selected results from the record of daily observations				
	8th Day	10th Day	12th Day	14th Day	16th Day
Effect of ordinary diet alone (detail omitted)					
Per cent	40	70	100	100	100
Effect of injecting 1 milligram/day of 4-amino-pteroylaspartic acid					
K23	sw	sw	pale	blue	large
K24	?	sw	blue	large	large
K21	....	sw	blue	large	large
K28	....	sw	blue	large	large
K29	....	sw	pale	blue	large
K30	....	sw	pale	blue	large
K25	....	sw	pale	blue	large
K22	....	sw	blue	large	large
K26	....	....	....	....	....
K27	....	....	....	....	....
Per cent	20	80	80	80	80
Effect of injecting 1 milligram/day of 4-amino-folic acid					
K11	....	....	....	....	....
K12	....	....	....	....	....
K14	....	....	....	....	....
K15	....	....	....	....	....
K18	....	....	....	....	....
K19	....	....	....	....	....
K13	....	....	....	....	sw
K17	....	....	....	sw	pale
K16	....	....	....	sw	pale
K20	....	....	sw	pale	blue
Per cent	0	0	10	30	40

sw: palpable swelling.
pale: slight blue discoloration.
blue: brilliant blue discoloration.
large: full size.

4-amino-pteroylaspartic acid. The test was made using seven weeks old chickens weighing about a pound and a half. The birds were given daily doses of 1 milligram of chemical from the time of inoculation with virus. The virus-inhibiting effect of this amount of 4-amino-pteroylaspartic acid was scarcely measurable while that of 4-amino-folic acid was clearly demonstrated. As shown by the use of the words "pale" and "blue" in the record of results, a prominent characteristic of the breast tumors in adult birds was the change of color from normal to brilliant blue.

It is of interest that the greater activity of 4-amino-folic acid was associated with a greater toxicity. Continuous injections of 1 milligram per day produced noticeable emaciation in the adult birds. The injection of a few doses of 10 micrograms killed baby chicks. Dr. J. J. Oleson of our laboratory found that at least 25 milligrams of folic acid were required to partially neutralize the toxicity of 1 mg. of the 4-amino-folic acid for rats. In an attempt to demonstrate the virus-inhibiting effect in baby chicks, we found that pteroyldiglutamic acid and pteroyltriglutamic acid also partially neutralized the toxicity of 4-amino-folic acid when used in the 25 to 1 ratio. Such mixtures showed no virus-inhibiting effect.

Discussion of Results. It has been repeatedly observed by us and various other groups that folic acid in the amounts given has by itself caused no induction of tumors. The particular activity of folic acid which we have described was exhibited only after the virus-infected cells had been transplanted. Also, in adult birds, even after the sarcoma has started to grow, anti-folic acids have prevented further growth; or, when sufficient numbers of cells have multiplied, the tumor growth can be inhibited. Thus, we were led to the tentative conclusion that, probably, the effect of these substances is on virus multiplication.

It is of interest that Waisman and associates (1945) found thiamine-deficient mice harder to infect with both Lansing poliomyelitis virus and Theiler's encephalomyelitis virus. It may be that virus, in contrast to bacteria, has to depend completely on the enzymatic systems of the host for its nutrition and multiplication. It may be that folic acid, in the case of Rous sarcoma virus, forms the prosthetic group of an enzyme vitally needed for the virus "metabolism." More examples of infection by virus and state of nutrition of the host will further clarify these points.

Summary

In our laboratory, Rous chicken sarcoma has been completely prevented by maintaining the birds on a synthetic, folic acid free diet from the time of inoculation with virus. Baby chicks were found to be more satisfactory for this demonstration than adult birds since the results were 100 per cent. Rous chicken sarcoma was also prevented by treating the birds with antagonists of folic acid (4-amino-folic acid, 4-amino-folic acid with d(—) glutamic acid, and 4-amino-pteroylaspartic acid). When treatment was delayed to permit sufficient development of cells, these antagonists of folic acid were able to prevent further growth of the sarcoma.

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USE OF FOLIC ACID DERIVATIVES IN THE TREATMENT OF HUMAN LEUKEMIA

By LEO M. MEYER*

Before embarking upon the presentation of my data, I wish first to acknowledge the active collaboration of Drs. Harold Fink, Norton Ritz, Manuel Rowen, and Arthur Sawitzky, without whose help their accumulation in so short a time would have been impossible. I also wish to emphasize the preliminary nature of this report, the purpose of which is to direct other investigators with similar interests into related channels. It is hoped that no misinterpretation of a panacea for leukemia or "cancer cure" is suggested by the few experiences which we have had in the last few months.

Doctors Boothe and Smith have reviewed the chemical nature and synthesis of some of the compounds which we have used, so that no repetition is necessary. Since the work is still current and not completely studied and analyzed, only a part of the data will be presented here.

Our first experience was with the use of teropterin or pteroyltriglutamic acid. Seven patients with chronic lymphocytic leukemia, two with chronic myeloid leukemia, two with multiple myeloma, and one with acute lymphoblastic leukemia were treated for periods of 4 to 10 weeks with doses ranging up to 200 mg. a day. A survey of the cases shows that, in chronic lymphocytic leukemia, no significant change occurred in the peripheral blood or bone marrow studies. In addition, no regression was observed in the size of the lymph nodes, spleen or liver. Clinically, however, most of the patients expressed an improvement in the sense of well-being, feeling stronger, and enjoying some increase in appetite. One striking case was noted in a man who was bed-ridden and emaciated. Following injections of teropterin up to 100 mg. b.i.d., he was able to get out of bed and began to gain in weight. He received no other supportive therapy. The patients with chronic myeloid leukemia had been in good condition, so that the clinical improvement was not so noticeable. No change in the peripheral blood or bone marrow was noted.

The most dramatic results were observed in the 2 cases with multiple myeloma. Patients who had been confined to bed, unable to move, and suffering considerable pain, were relieved of their symptoms in 2 to 3 weeks and were able to get out of bed. I should like to emphasize, however, that there were no changes in the bone marrow studies or skeletal x-rays in this group. The improvement was entirely subjective.

The patient with acute lymphoblastic leukemia deserves to be presented in more detail. E.T., an adult white female, age 55, was under my care for 6 weeks before her present admission to the New York Hospital. Her chief complaints were pallor, weakness, bleeding gums, and purpura. A diagnosis of acute lymphoblastic leukemia had been made. She was treated with a filtrate of potato juice and ascorbic acid, as suggested by Isaacs, but no clinical or hematologic improvement was noted. At the New York Hospital, her blood count disclosed 32,700 leucocytes, of which 77 per cent were lymphoblasts and 18 per cent mature lymphocytes. Patient was started on 20 mg. teropterin intramuscularly, daily. The dosage was increased up to 100 mg. daily and later to 100 mg. b.i.d. There was a period about 6 weeks after the institution of therapy when the leucocyte count dropped to between 14 and 20,000. The more significant change, however, was the gradual fall in the number of blast cells and the coincident rise in mature lymphocytes. This change in peripheral blood was reflected in the bone marrow. Here, the blasts fell from 31 to 17 per cent and the lymphocytes rose from 66 to 81 per cent. Clinically, the patient had an episode of otitis media which was controlled with the use of penicillin. Destruction of the drum occurred. There

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was also infiltration of both retinae, which reduced the patient's vision. However, the temperature gradually returned to normal and the patient became ambulatory. The spleen slowly enlarged and was felt 2 cms. below the left costal border. The final clinical picture suggested a chronic lymphocytic leukemia. The patient was allowed to go home for the Thanksgiving holiday; that weekend she had several attacks of severe left upper quadrant pain which were interpreted as due to splenic infarction. She expired in 24 hours and no autopsy was obtained. The last blood count was 55,000 leucocytes, of which 90 per cent were mature lymphocytes.

Dr. Franklin Miller, of Philadelphia, has given me permission to present briefly a summary of his experience with diopterin or pteroyldiglutamic acid, in a case of acute lymphoblastic leukemia. This patient was treated from February, 1946, to September, 1947, with brewer's yeast daily, and transfusions were made every 2 weeks. On the last date, the leucocytes rose from 10,000 to 34,000 and the blast cells increased from 15 to 80 per cent. The patient was started on 50 mg. of diopterin intramuscularly, daily. About 3 weeks later, the total white cell count fell to 5,000 per cu.mm. and the blasts were reduced to 8 per cent. The remainder of the cells were mainly mature small lymphocytes. The patient required less frequent transfusions and the temperature, which had risen when the leucocytosis occurred, came down to normal.

In the group of anti-folic acid compounds, the most significant results to be reported are those in 5 cases of acute leukemia, all of whom showed somewhat similar findings.

J.L. a white male, age 6, was admitted to the King's County Hospital because of poor appetite, fatigability, and frontal headaches of one week's duration. Physical examination showed multiple petechiae, cervical, axillary and inguinal lymphadenopathy, splenomegaly, and hepatomegaly. The blood picture was that of an acute myeloblastic leukemia.

On admission, the total white cell count was 500,000, of which 99 per cent were myeloblasts. An-Fol-R* was started in doses of 20 mg. intramuscularly, daily. Six days later, the dose was increased to 40 mg. The total leucocytes fell from the extremely high level to 7,500 and the blood picture changed from 99 to 2 per cent blasts, and segmented leucocytes rose to a peak of 70 per cent. At this time, there was a complete regression of nodes, liver, and spleen. It was during this period that the patient suffered a cerebral accident involving the pons. His condition was critical, but he survived; as a result, he became blind. The reduction in count was short-lived and white cells began to climb. The dose of An-Fol-R was doubled, but there was no improvement. The medication was changed and the patient was given 20 mg. of Met-Fol-B,† which was increased to 40 mg. daily and, finally, to 40 mg. b.i.d., but the total leucocytes continued to rise and blast cells reappeared to the extent indicated. The lymphadenopathy, splenomegaly, and hepatomegaly recurred. The bone marrow showed a slight reduction in blast cells but not comparable to that seen in the peripheral blood. When the total leucocytes rose again, the blast cells increased in the bone marrow.

H.J. a negro female, age 76, was admitted to the hospital because of extreme weakness. On physical examination, a large thyroid was noted. X-ray of the chest showed a substernal thyroid and large traction diverticulae of the esophagus. The blood picture was that of an acute myeloblastic leukemia. The total leucocytes were 150,000, with 68 per cent myeloblasts. Patient was placed on 40 mg. Met-Fol-B, daily. This was increased to

* Cryptic name for *N*-[4-{[(2-amino-4-hydroxy-6-pteridyl)methyl]amino}-benzoyl]*d,l*-aspartic acid.

† Cryptic name for 4-{*N*-[(2-amino-4-hydroxy-6-pteridyl)methyl]-*N*-methylamino}benzoic acid.

b.i.d. in 3 days. The total leucocytes fell from 150,000 to 1,500 in 12 days. The blasts came down to between 40 and 52 per cent. The polymorphonuclears were only slightly increased to 8 per cent and mature lymphocytes rose at this time to 34 per cent. When the leucocytes fell to 1,500, the dosage was reduced to 20 mg. b.i.d. However, when the white blood count began to increase, the dose was raised to 40 mg. b.i.d. and then 80 mg. b.i.d., but this did not affect the rising count. With the increase in total leucocytes, the blast cells also rose in number. The bone marrow reflected the peripheral leucopenia in that the total nucleated cell count fell from 150,000 to 28,000 and the blasts from 80 to 46 per cent. Within 3 days, however, there was evidence of a rising total nucleated cell count and blasts.

About one week ago, the patient was started on a third anti-folic acid compound which appeared to be producing a second reduction in total cells. However, she died last Friday of her disease and the efficacy of this derivative could not be ascertained.

D.F., a negro boy, age 6, was admitted to the hospital because of weakness and severe migratory joint pains. A diagnosis of acute rheumatic fever was entertained, but the blood counts and bone marrow disclosed an acute myeloblastic leukemia. Except for the tender, painful joints and splenomegaly 2 cm. below the costal border, examination was not remarkable. Several blood counts showed leucocytes ranging from 5 to 10,000. On the day treatment was started, the white blood cells were counted at 5,500 with 19 per cent myeloblasts, 3 per cent myelocytes, 8 per cent metamyelocytes, 9 per cent non-segmented neutrophiles, and 22 per cent segmented forms. Patient was given 20 mg. Met-Fol-B daily. This was increased to 20 mg. b.i.d. in 3 days, and 3 days later the dose was increased to 40 mg. b.i.d. There was a slight but persistent leucopenia which rose slowly again to a figure close to the pre-treatment level. However, the total number of immature cells was reduced to 8 per cent and the more mature forms were increased to 19 per cent bands and 36 per cent segmented forms. Except for a severe nose-bleed which the patient suffered around Nov. 23, the general condition has remained fair. The joint pains have disappeared and the spleen and liver are now palpable 2-3 cm. below the costal border.

M.M., an adult white male, age about 30, was admitted to the hospital from another institution with the diagnosis of acute myeloblastic leukemia. The patient's major complaints were weakness, pallor, and swollen, spongy gums of about 6 weeks' duration. The initial blood count showed 36,000 leucocytes of which 17 per cent were myeloblasts, 38 per cent myelocytes, and 16 per cent segmented and non-segmented forms. The patient was started on 20 mg. An-Fol-R daily. This dose was doubled 7 days later. 23 days after treatment was begun, we ran out of medication and the patient received no therapy for 3 days. Thereafter, he was given 40 mg. Met-Fol-B daily which was increased in 72 hours to 80 mg. a day. The most significant findings in his blood are the reduction in myeloblasts to 1 per cent from 17 per cent, myelocytes from 38 to 26 per cent, and an increase in segmented and non-segmented neutrophiles from 16 to 40 per cent. The changes in the total white cell count are not so striking as in the 3 previous cases, but this may be due to the fact that these counts were taken by different persons, and we are all aware of the errors inherent in such a procedure. However, all of the differential studies were made by one observer.

The bone marrow shows a similar trend. On admission, the blasts were 42 per cent, myelocytes 18 and segmented neutrophiles 2 per cent. One month after treatment, the blasts were reduced to 4 per cent, myelocytes increased to 67 per cent, and neutrophiles up to 17 per cent. Clinically, the patient feels much improved. In fact, early last month he wanted to leave the hospital to go bear-hunting. There has been considerable regression of the swell-

ing of the gums, but they are by no means normal. During the past 2-3 weeks, the patient has had several attacks of bilateral peri-tonsillar abscesses which have been well controlled with pencillin.

R.L., an adult white male, age 21, was admitted to the hospital because of weakness and pallor of about 1 week's duration. Except for his pallor, the physical examination was not remarkable. The blood count revealed 5,000 white cells, of which 30 per cent were myeloblasts and 30 per cent myelocytes. He was started on 20 mg. An-Fol-R daily, which was increased in 2 weeks to 40 mg. After 1 month, the drug was discontinued for 3 days, following which Met-Fol-B therapy was begun, in doses of first 40 mg. and then 80 mg. daily. A review of the blood smears shows a significant reduction in the number of myeloblasts with an increase in the myelocytes. The number of mature polymorphonuclear leucocytes did not change. Again, the variations in total white cells may be due to the technique, as the counts were taken by different technicians. However, the differential smears were studied by one observer. In the bone marrow, the changes are more striking. The myeloblasts have been reduced from 49 to 1.5 per cent and the myelocytes increased from 22 to 82 per cent. Clinically, the patient has been critically ill for short periods, but each time he has recovered, due largely to transfusions and antibiotic therapy. Between infections—if these are infections—he appears quite well and is ambulatory. At present, he is very ill with a pneumonia which followed a severe sore throat.

In addition to these 5 patients with acute leukemia treated with anti-folic acid compounds, we wish to report that we have had 3 patients with chronic lymphocytic leukemia under our care for 4-6 weeks, using Met-Fol-B in doses of 40 mg. b.i.d., who have shown no hematological improvement. The patients state, however, that they feel better and enjoy a sense of well-being.

In summary, we have treated acute and chronic leukemia, as well as multiple myeloma, for varying periods of time, using derivatives of folic acid. In general, regardless of the compound, if treated for periods over 2-3 weeks, the patients appear to feel better, eat more, and in the cases of myeloma have relief from pain. In the cases of chronic leukemia and multiple myeloma, no alteration in blood picture or bone marrow took place. It has not been our experience to see frequent spontaneous reductions in the number of blast cells in acute leukemia. In the cases reported, using teropterin and diopterin, the lymphoblasts were replaced by mature lymphocytes. This is completely different from the reaction following radiation or nitrogen mustard therapy. With the anti-folic acid compounds, there was a reduction in the total white cells in 3 cases, with a temporary shift to the right. This remission, though short-lived, suggested an alteration or interference with the metabolism or chemical reaction in the malignant cells. In 2 cases of acute leukemia, there has been a persistent shift to the right.

Again, I wish to emphasize the preliminary nature of this report. The purpose has been solely to acquaint other investigators with our findings, so that we may be of mutual help in our work. I believe that the data are suitable only for distribution to that portion of the medical profession actively engaged in this work.

DISCUSSION

By ALFRED GELLHORN*

In the series of papers presented here, the only objective evidence that folic acid has a carcinolytic effect, was, it seems to me, cited in the historical review by Dr. Waller. In this paper, the observations of Dr. Lewisohn and his associates at Mount Sinai Hospital were referred to. It will be recalled that these investigators found that

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protracted intravenous administration of folic acid resulted in the disappearance of spontaneous adenocarcinoma of the breast in mice in as high as 30 per cent of the experimental group. Dr. Waller failed to mention, however, that this experimental observation has not been confirmed although an extensive investigation by Dr. Sugiura at the Memorial Hospital was carried out in an attempt to verify it.

Very briefly, I should like to comment on the clinical evaluation of teropterin in the therapy of human neoplastic disease. In Dr. Klainer's report of a single case of carcinoma of the breast with osseous metastases, it seems to me very important to note the therapy given in addition to teropterin. As I recall, the patient received 100-150 mg. of testosterone propionate daily for one month and, in addition, was surgically castrated. Adair and Hermann at the Memorial Hospital have reported the results of testosterone therapy in a large series of patients with just such lesions as existed in Dr. Klainer's case. Adair and Hermann found that relief of pain and, not infrequently, x-ray evidence of bone healing occurred in a large percentage of their patients following the administration of as little as 2400 mg. of testosterone propionate. The duration of remission induced by such androgen therapy was, in some instances, as long as eighteen months. I believe, therefore, that, in the evaluation of teropterin therapy in Dr. Klainer's patient, the fact should be stressed that she also received other forms of treatment which could be expected to produce the remission noted.

In the series of patients presented by Dr. Lehv, in only one possible instance was there objective evidence that a fundamental alteration of the course of the disease had been produced by teropterin therapy. This was the patient with carcinoma of the prostate, with evidence of neurologic involvement by metastases, who had an improvement of his neurological signs and symptoms following therapy with pteroyltriglutamic acid. The results, even in this case, were equivocal due to the fact that an orchidectomy had been performed prior to the administration of teropterin. In all the other patients, it appeared that the course of the disease had in no way been altered. Dr. Lehv stated that serial biopsies were taken on a number of the cases, but no mention was made of morphological changes in the neoplasms. It is, however, tremendously interesting that, in Dr. Lehv's patients as well as those of Dr. Meyer, a sense of well-being and an apparent analgesic effect were produced. In this connection, it is to be recalled that Dr. Waelsch and his associates at the Psychiatric Institute have shown that glutamic acid has an anticonvulsive effect in *petit mal* epilepsy and also favorably affects cortical function in feeble-minded children. This suggests the possibility that the subjective improvement noted by the patients on teropterin therapy was due to a central nervous system effect of the drug related to the pharmacological action of glutamic acid. Admittedly, the dosages of glutamic acid employed by Dr. Waelsch were of an entirely different order of magnitude than the amount present in teropterin; however, the peptide linkage of the glutamic acids in teropterin might alter its distribution and effect.

In the patients with leukemia treated by Dr. Meyer, it again appears that the course of the disease was not significantly altered by teropterin. To be sure, in several of these patients there was a change in the peripheral blood picture with a decrease in the number of blasts and other immature forms. However, this sort of change frequently occurs spontaneously in acute leukemia and has also been induced repeatedly with radiotherapy or nitrogen mustard. It has been demonstrated that these latter two therapeutic regimes do not favorably influence the outcome of the disease, and it does not seem to me that evidence has been presented which would indicate that teropterin has actually achieved more than a temporary effect.

REPORT OF THE ANNUAL MEETING

December 17, 1947

The 130th Annual Meeting of the Academy, for the election of Officers and Fellows, the presentation of reports, and the transaction of other business was held at the Hotel Astor on the evening of Wednesday, December 17, 1947.

The first order of business was the presentation for final vote of the revised Constitution of the Academy. This revision, which is intended to adapt the basic organization of the Academy to present conditions, was unanimously adopted in the form presented below.

THE CONSTITUTION OF THE NEW YORK ACADEMY OF SCIENCES

(as revised and adopted at the Annual Meeting of the Academy, December 17, 1947 effective as of this date).

ARTICLE I. The name of this Corporation shall be The New York Academy of Sciences. Its object shall be the advancement and diffusion of scientific knowledge, and the center of its activities shall be in the City of New York.

ARTICLE II. The Academy shall consist of six classes of members, namely: Life Members, Sustaining Members, Annual Active Members, Student Members, Honorary Life Members, and Corporation Members. The designation Active Member shall be applied to all voting members of the Academy which shall include all the above classes except Student Members, Honorary Life Members, and Corporation Members. Active Members of the Academy, outstanding in virtue of their scientific attainments, may be chosen to become Fellows of the Academy. Honorary Life Members shall be chosen from among persons who have attained distinction in some branch of science. The number of Honorary Life Members shall not exceed one hundred.

ARTICLE III. None but those Active Members of the Academy who have paid their dues up to and including the preceding fiscal year shall be entitled to vote or shall be eligible to hold office in the Academy.

ARTICLE IV. The officers of the Academy shall be a President, two Vice-Presidents, a Corresponding Secretary, a Recording Secretary, a Treasurer, an Editor, nine elected Councilors, a Finance Committee of three, and the Chairman of each established Section of the Academy. The annual election of these officers shall be held on the third Monday in December, or on some other day in December specifically designated by vote of the Council, the officers then chosen to take office on the first day of January following.

An Executive Director shall be elected annually by the Council, at its first meeting in January, for a term of one year, beginning with the first day of February following, or until his successor shall have been chosen.

ARTICLE V. The officers of the Academy named in Article IV shall constitute a Council, which shall be the executive body of the Academy with general control over its affairs, including the establishment, division, subdivision or discontinuance of Section of the Academy and the power to fill *ad interim* any vacancies in the offices. Past Presidents of the Academy shall be invited annually to serve as members of the Council and, upon their acceptance of the invitation, they shall be

ex-officio members of the Council for the following calendar year and eligible for a renewal of such invitation by order of the Council.

ARTICLE VI. The Council shall have the power to establish or discontinue affiliation of scientific societies or associations, organized for the study of any branch of science, with The New York Academy of Sciences. Members of allied societies may become Active Members of the Academy upon election by the Council and upon payment of the fee prescribed for such membership, otherwise as members of an allied society they shall be entitled to such privileges as shall be determined by the Council of the Academy. Each allied society shall have the right to delegate one of its members, who is also an Active Member of the Academy, to the Council of the Academy, and such delegate shall have all the rights and privileges of other Councilors.

ARTICLE VII. The President, Vice-Presidents and Sectional Chairmen shall not be eligible to more than one re-election. The Secretaries, Treasurer, Editor and Members of the Finance Committee shall be eligible to re-election without limitation. The President, Vice-Presidents and Secretaries shall be Fellows. The terms of office of elected Councilors shall be three years, and these officers shall be so grouped that three, at least one of whom shall be a Fellow, shall be elected and three retired each year. Elected Councilors shall not be eligible to re-election until after the expiration of one year.

ARTICLE VIII. The election of officers shall be by ballot, and the candidates having the greatest number of votes shall be declared duly elected.

ARTICLE IX. Ten Active Members shall form a quorum at any meeting of the Academy at which business is transacted.

ARTICLE X. The Council shall establish such by-laws, not in conflict with the Constitution, as may be necessary for the proper government of the Academy and may amend them from time to time as therein provided.

ARTICLE XI. This Constitution may be amended by a vote of not less than three-fourths of the Active Members present and voting at a stated business meeting of the Academy, provided that the Recording Secretary shall send a copy of the proposed amendment, at least two weeks before the meeting, at which a vote shall be taken, to each Active Member entitled to vote.

REPORTS OF OFFICERS AND COMMITTEES

The Recording Secretary, in his report, drew the attention of the Members of the Academy to the time and energy absorbed in planning, preparation and organization, before the regular meetings and conferences of the Academy can be held with their extensive series of scientific reports and discussions. Likewise, after the meetings are over, there comes a difficult period of revising, assembling and editing the papers, in order to bring about publication and final distribution.

It would be difficult to list individually the participating scientists, the Committee and Council Members, as well as the Academy's employed staff, in acknowledging our indebtedness for their wholehearted and assiduous support of this Society. However, special thanks are due to those who have been outstanding in their services for making possible this successful year in the Academy's history.

Appreciation is expressed to Doctor Hans Molitor for his many services to the Academy not only as a Councilor but as Chairman of the Rules Committee while

it was engaged in the study and revision of the Constitution of the Academy.

The Chairmen and Secretaries of the various Sections have maintained a high standard in selecting scientific material for the programs of the evening meetings.

Doctors Ross F. Nigrelli and Charles R. Schroeder, of the Section of Biology, have steered nine of the ten conferences, held this year, through to success. The officers of the Section of Psychology, Doctors S. Stansfeld Sargent and Clairette P. Armstrong, managed an outstanding conference in the field of clinical psychology.

Doctor Myron Gordon, Organizing Chairman of the Conference on Melanomas, not only has served as Consulting Editor of the volume now forthcoming on *"The Biology of Melanomas,"* but in addition has obtained $10,500 in five separate grants-in-aid toward the publication costs of this important work.

Through the efforts of Doctors Fredrick F. Yonkman, Carl A. Dragstedt and Y. SubbaRow, sufficient funds were secured to enable the Academy to bring to this country Sir Henry H. Dale, London, England; Doctor Daniel Bovet, Rome, Italy; Doctor M. Roche e Silva, Sao Paulo, Brazil; Doctor Rolf Meier, Basel, Switzerland; and Doctor E. T. Waters, Toronto, Canada, as well as the other speakers on the program of the Conference on *"Antihistamine Agents in Allergy."*

Thanks are due to Doctor Charles Glen King and Doctor Philip S. Owen for facilitating support for both the Conference and publication on *"Nutrition in Relation to Cancer,"* which was sponsored jointly by the Academy and the Panel on Nutrition, Committee on Growth, of the National Research Council.

We wish to acknowledge the hospitable cooperation of The New York Academy of Medicine through the courtesy of its President, Doctor George Baehr, and its Director, Doctor Howard Reid Craig, on the occasion of the Conference on *"The Adrenal Cortex,"* jointly sponsored by The New York Academy of Sciences and The New York Academy of Medicine, in recognition of the Centennial Celebration of the latter Society.

The titles of the seven additional Conferences held are as follows: Section of Biology—*"The Mechanics of Development," "Thyroid Function as Disclosed by Newer Methods of Study," "Allergy," "Structure in Relation to Cellular Function," "The Chemotherapy of Filariasis,"* and *"Medical Mycology";* Section of Psychology—*"Current Trends in Clinical Psychology."*

Nine Life Members, 22 Sustaining Members, 1,045 Annual Active Members, 47 Associate Members and 43 Student Members were added to the rolls, of which 1,114 are now in good standing and 52 await qualification through payment of dues. Thus, a total of 1,166 new Members was added during the year. One Annual Active Member was transferred to Life Membership by payment of the Life Membership fee. Fifty-four transfers and 21 reinstatements were also effected between the various classes of Membership, with the approval of the Council.

The Academy has lost by death 5 Honorary Life Members, 4 Life Members, 5 Sustaining Members, 10 Annual Active Members, and 5 Associate Members. Sixty-two resignations were accepted, 57 names were dropped for non-payment of dues, and 3 for not having qualified for membership.

The record now stands with a net gain of 1,035 Members. There are, at present, upon the rolls of the Academy 4,009 Members, of whom 456 are Fellows.

The report of the Corresponding Secretary showed that, due to the death of five Honorary Life Members, recorded with regret, the number upon the rolls of the Academy was reduced from 49 to 44 during the past year.

The Editor reported that, during the fiscal year of 1947, the Academy pub-

lished a total of 1,918 pages. Of these, 1,098 pages appeared in the Annals (8 articles) and 478 pages in the Special Publications, including 87 papers by 118 authors. A total of 342 pages were published in the Transactions. In addition to the Annals published this year, Article 2 of Volume 49 is in press, to be issued shortly. A number of other articles are in process of editing and will be published during the coming year in Volumes 49, 50, and 51. Volume 17, Part I of the Scientific Survey of Porto Rico and the Virgin Islands is also in the Editor's hands and will be issued soon.

The detailed list of those publications which have appeared this year is as follows:

ANNALS

Volume 46, Article 10, *"Brain and Body Weight in Man"* (1 paper), by Earl W. Count. Pages 993–1122. Published January 15, 1947.

Volume 47, Article 5, *"Physiological and Psychological Factors in Sex Behavior"* (6 papers), by S. Bernard Wortis, Gregory Bateson, William E. Galt, Morris Herman, Alfred C. Kinsey, and William C. Young. Pages 603–664. Published May 9, 1947.

Volume 47, Article 6, *"Muscular Contraction"* (12 papers), by Alexander Sandow, R. S. Bear, Ernst Fischer, A. S. Gilson, Jr., Eugene Guth, C. E. Hall, M. A. Jakus, S. W. Kuffler, Otto Meyerhof, Severo Ochoa, Robert W. Ramsey, F. O. Schmitt, G. M. Schoepfle, Shih-Chang Shen, H. Burr Steinbach, and S. M. Walker. Pages 665–930. Published May 30, 1947.

Volume 48, Article 5 (Supplement), *"The Synthesis of Pteroylglutamic Acid (Liver* L. Casei *Factor) and Pteroic Acid—Part II"* (1 paper), by M. E. Hultquist, Robert B. Angier, James H. Boothe, Donna B. Cosulich, M. J. Fahrenbach, Brian L. Hutchings, Erwin Kuh, John H. Mowat, E. H. Northey, Doris R. Seeger, Joseph Semb, J. P. Sickels, James M. Smith, Jr., E. L. R. Stokstad, Y. SubbaRow, and Coy W. Waller. Pages i–vi. Published October 3, 1947.

Volume 48, Article 6, *"The Relation of Diseases in the Lower Animals to Human Welfare"* (10 papers), by William A. Hagan, Herald R. Cox, William H. Feldman, I. Forest Huddleson, Harald N. Johnson, Raymond A. Kelser, Joseph V. Klauder, Karl F. Meyer, C. D. Stein, and Willard H. Wright. Pages 351–576. Published April 10, 1947.

Volume 48, Article 7, *"Some Aspects of Red Cell Production and Destruction"* (6 papers), by Eric Ponder, William B. Castle, Harry A. Charipper, William Dameshek, Albert S. Gordon, S. Granick, and F. S. Robscheit-Robbins. Pages 577–704. Published July 3, 1947.

Volume 48, Article 8, *"Convection Patterns in the Atmosphere and Ocean"* (11 papers), by R. B. Montgomery, John C. Armstrong, Horace R. Byers, Phil E. Church, Richard A. Craig, B. Haurwitz, Walter H. Munk, Henry Stommel, Harry Wexler, Raymond Wexler, A. H. Woodcock, and Jeffries Wyman. Pages 705–844. Published September 15, 1947.

Volume 49, Article 1, *"Nutrition in Relation to Cancer"* (12 papers), by Charles Glen King, John J. Bittner, D. H. Copeland, R. W. Engel, C. J. Kensler, George W. Kidder, G. Burroughs Mider, J. A. Miller, Harold P. Morris, William J. Robbins, W. D. Salmon, Albert Tannenbaum, E. L. Tatum, Florence R. White, Julius White, and Philip R. White. Pages 1–140. Published September 7, 1947.

SPECIAL PUBLICATIONS

Volume IV, *"The Biology of Melanomas"* (28 papers), by Myron Gordon, Glenn H. Algire, S. William Becker, Harold F. Blum, Liane R. Brauch, E. A. Sheremetieva-Brunst, V. V. Brunst, Dean Burk, Gladys Cameron, Graham Philips DuShane, Frank H. J. Figge, Clara E. Fisher, Denis L. Fox, Samuel A. Goldberg, C. G. Grand, Jesse P. Greenstein, James B. Hamilton, R. G. Harrison, Marie L. Hesselbach, M. J. Kopac, Frances Y. Legallais, Michael Levine, Eleanor J. Macdonald, Madge Thurlow Macklin, Howard S. Mason, P. Masson, J. M. Odiorne, George T. Pack, Elizabeth S. Russell, W. L. Russell, Leonell C. Strong, Kanematsu Sugiura, Helenor Campbell Wilder, and B. H. Willier. Pages i–xii, 1–466. This is now being printed as a cloth-bound volume, and will appear about January 1, 1948.

TRANSACTIONS

Series II, Volume 9, Nos. 1–8, consisting of 342 pages, was completed, printed and distributed each month from November, 1946, to June, 1947, inclusive.

The Librarian reported that, during the year 1947, the Academy distributed 74,560 separate publications and 6,788 complete volumes of the various published series, as follows:

Separate Numbers—*Annals,* 64,111; *Scientific Survey of Porto Rico and the Virgin Islands,* 415; *Transactions,* Series II, 7,023; *Memoirs,* 49; *Bulletins,* 2,962.

Volumes—*Annals,* 376; *Annals of the*

Lyceum, 1; *Scientific Survey of Porto Rico and the Virgin Islands,* 171; *Special Publications,* 1,065; *Transactions,* Series I, 145, and Series II, 115; *Bulletins,* 4,915.

During the present year, ten complete sets of the publications of the Academy were sent to the Philippines and China to aid in rebuilding institutional libraries destroyed during the war. This brings the total to 18 sets donated by the Academy for this purpose. In addition, a complete set of our publications has been presented to the Library of the United Nations Organization. The institutions, throughout the world, with which the Academy exchanges or in which it deposits its publications, have now been brought up to date in this respect.

The Academy has received, from its exchange institutions, 2,415 separate publications, which have been duly turned over to the Library of The American Museum of Natural History, in accordance with the agreement between the two institutions.

The total value of publications distributed gratis to the members, authors and exchange institutions is $40,326.43.

The Treasurer reported that the Academy, while pursuing its established program of progressive activities in the field of science, also exhibits a corresponding financial development, continuing the progress of recent years. During the fiscal year ending November 30, 1947, receipts from all sources totaled $84,611.57. The disbursements amounted to $77,042.59.

New Members elected during the year totaled 1,166, in addition to 21 reinstatements. The receipts from this source include $1,000.00 for 10 Life Memberships which was added to the Permanent Fund, thus increasing the endowment of the Academy to that extent.

Receipts from sales of publications and library exchanges amounted to $25,247.64.

Mr. William Otis Sweet contributed $1,000.00 to be added to the fund established in his name, from the capital of which he also donated a grant-in-aid of $1,500.00, in support of the Academy's publication program.

The Treasurer also wishes to acknowledge with gratitude and appreciation, on behalf of the Academy, twenty-one donations or grants totaling $25,420.93, received during 1947, to aid in defraying both conference and publication expenses, as follows: American Cancer Society, $5,000; American Cyanamid Company, $3,400.06; Ciba Pharmaceutical Products, Inc., $400.00; Ciba Ltd., Canada, $100.00; Jane Coffin Childs Memorial Fund for Medical Research, $1,000.00; Anna Fuller Fund, $1,000.00; Hoffman-La Roche, Inc., $400.00; Merck and Company, $400.00; Department of Agriculture and Commerce, Puerto Rico, $3,000.00; National Cancer Research Institute, $3,000.00; National Research Council, Panel on Growth, $804.87; The Nutrition Foundation, Inc., $1,699.00; Parke, Davis and Company, $400.00; The Rockefeller Foundation, $1,500.00; E. R. Squibb and Sons, $400.00; William Otis Sweet, $1,000.00 (plus $500 transferred from the capital of the Sweet Fund); University of Puerto Rico, $1,500.00; The Upjohn Company, $400.00; sundry contributions for Publication Fund, $17.00.

The Finance Committee, acting in an advisory capacity to the Treasurer in the matter of investments, through the sales of certain stocks produced a net capital gain of $8,649.98. Of this amount, $5,135.23 was allocated to cover the cost of the preliminary survey made on behalf of the Academy by the firm of Tamblyn and Brown, Inc. The balance, $3,514.75, was used to aid in covering publication costs. The interest on investments amounted to $5,198.46, representing a yield of 5.6%.

The book value of the Academy's investments and cash on hand, as of November 30, 1947, now amounts to $104,376.39, as shown on the balance sheet.

By order of the Council, the books of

account have been checked and audited by a professional firm of auditors. The financial report of the Academy has been approved by the Finance Committee as provided in the By-Laws.

The property of the Academy was verified by the auditor and the Finance Committee, and the Treasurer's report examined and attested by the Finance Committee as of December 11, 1947.

AWARD OF A. CRESSY MORRISON PRIZES

The A. Cressy Morrison Prize of $500.00 for the best paper on the sources of solar and stellar energy was awarded to the paper entitled: *"Energy Sources in Giant Stars,"* by Donald H. Menzel, Harvard Observatory, Harvard University, Cambridge, Massachusetts.*

A prize of $200.00 for the most acceptable paper in a field of Natural Science covered by the Academy, or an Affiliated Society, was awarded to the paper entitled: *"The Effect of* Clostridium tetani *Toxoid in the Relapse of Malaria,"* by Eusebio Y. Garcia, Medical Research Clinic, Binan, Laguna, Republic of the Philippines.*

The Prize Committee takes pleasure in announcing, on behalf of Mr. Morrison, that he has again offered two prizes, of $200.00 each, for the two most outstanding papers in a field of science covered by the Academy or an Affiliated Society, to be competed for during the year 1948. Announcement of these awards will be made at the Annual Meeting of the Academy, to be held in December, 1948. Final announcement of the terms of this competition will be made in the February issue of the Transactions and special circulars will also be sent to members of the Academy and its Affiliated Societies.

ELECTION OF FELLOWS AND HONORARY LIFE MEMBERS

The following Members were elected to Fellowship:

Mark H. Adams, Ph.D.
Mildred Adams, Ph.D.
John A. Aeschlimann, Ph.D.
Turner Alfrey, Jr., Ph.D.
James B. Allison, Ph.D.
John C. Armstrong, Ph.D.
Lester R. Aronson
Reginald Auchincloss, Ph.D.
Robert Ballentine, Ph.D.
W. Dexter Bellamy, Ph.D.
Gerrit Bevelander, Ph.D.
Isabel H. Blount, Ph.D.
Raymond F. Blount, Ph.D.
Stuart R. Brinkley, Ph.D.
Alice I. Bryan, Ph.D.
Victor Carabba, M.D.
Benjamin W. Carey, M.D.
Robert Chambers, Ph.D.
George R. Cowgill, Ph.D.
F. J. Crane, D.Sc.
Harry E. Crum
Gaetano F. D'Alelio, Ph.D.
Charles R. Dawson, Ph.D.
Herman W. Dorn, Ph.D.
Fred W. Dunihue, Ph.D.
Max S. Dunn, Ph.D.
T. H. Eaton, Jr., Ph.D.
William F. Ehret, Ph.D.
Robert K. Enders, Ph.D.
Jackson P. English, Ph.D.
William O. Field, Jr., B.S.
Ella Fishberg, M.D.
Charles N. Frey, Ph.D.
James P. Fugassi, M.D.
Ellis J. Fulmer, Ph.D.
Arthur I. Gates, Ph.D.
Robert Gaunt, Ph.D.
Alfred Gellhorn, M.D.
A. E. Gessler, Ph.D.
Willis A. Gibbons, Ph.D.
Alfred Gilman, Ph.D.
Harry Gold, M.D.
Harry Goldblatt, M.D.
Max A. Goldzieher, M.D.
Louis S. Goodman, M.D.
Aubrey Gorbman, Ph.D.

* For abstracts of both prize papers, see pp. 125-6 of this number of TRANSACTIONS. The paper by Dr. Garcia will be published, in full, as ANNALS, Volume 50, Article 2.

Sam Granick, Ph.D.
Roy O. Greep, Ph.D.
Arthur Grollman, Ph.D.
Rudolf E. Gruber, Sc.D.
Harry Grundfest, Ph.D.
Walter J. Hamer, Ph.D.
Ben King Harned, Ph.D.
Henry H. Hausner, D.E.
Roderick Heffron, M.D.
Harold E. Himwich, M.D.
Charles B. Hitchcock, M.A.
Hudson Hoagland, Ph.D.
Seymore Hochberg, Ph.D.
Jorgen Holmboe, M.S.
John C. Hostetter, Sc.D.
Seymour H. Hutner, Ph.D.
Carl Iddings, Ph.D.
Thomas H. James, Ph.D.
Herbert H. Jasper, Ph.D.
Thomas H. Jukes, Ph.D.
Francois Kertesz, Sc.D.
Roy H. Kienle, Ph.D.
Helen D. King, Ph.D.
Israel S. Kleiner, Ph.D.
Hilary Koprowski, M.D.
Gertrude Kornfeld, Ph.D.
Lawrence S. Kubie, M.D.
Marvin H. Kuizenga, Ph.D.
Raphael Kurzrok, M.D.
Willis E. Lamb, Jr., Ph.D.
Alexander D. Langmuir, M.D.
James Hain Leathem, Ph.D.
Philip Levine, M.D.
Howard B. Lewis, Ph.D.
Raymond L. Libby, Ph.D.
Urner Liddel, Ph.D.
John R. Loufbourow, Sc.D.
John K. Loosli, Ph.D.
Lawson G. Lowrey, M.D.
William H. McCastline, M.D.
Philip D. McMaster, M.D.
Thomas L. McMeekin, Ph.D.
Benjamin Malzberg, Ph.D.
Paul V. Manning, Ph.D.
Louis W. Maraventano, M.D.
Henry C. Marks, Ph.D.
Charles A. Marlies, Ph.D.
Joseph Mattiello, Ph.D.
Nicholas A. Milas, Ph.D.
John A. Moore, Ph.D.
Robert S. Morison, M.D.
John H. Mulholland, M.D.
Otto H. Muller, Sc.D.
Carl Neuberg, Ph.D.
Leslie F. Nims, Ph.D.
Friederich F. Nord, D.Sc.
Byron J. Oakes, Ph.D.
Fairfield Osborn
Gerald Oster, Ph.D.
Raymond C. Parker, Ph.D.
Arthur L. Patterson, Ph.D.
Ely Perlman, M.D.
Jean Piatt, Ph.D.
Zygmunt Anthony Piotrowski, Ph.D.
Bret Ratner, M.D.
Jonathan E. Rhoads, M.D.
Walter S. Root, Ph.D.
Harry M. Rose, Ph.D.
Antonio Rottino, M.D.
E. A. Rovenstine, M.D.
John B. Russell, M.S.
Amram Scheinfeld
Maxwell Schubert, Ph.D.
Jack Schultz, Ph.D.
Ervin Schwenk, D.Sc.
Morton D. Schweitzer, Ph.D.
Leo Shedlovsky, Ph.D.
Simon Shlaer, Ph.D.
Ephraim Shorr, M.D.
H. O. Singher, Ph.D.
Harry H. Sobotka, Ph.D.
David M. Spain, M.D.
Herman T. Spieth, Ph.D.
Henry B. Steinbach, Ph.D.
Y. SubbaRow, Ph.D.
Percival M. Symonds, Ph.D.
Maurice L. Tainter, M.D.
William Thalhimer, M.D.
Hans E. Thalmann, Ph.D.
Henry C. Thomas, Ph.D.
Max Tishler, Ph.D.
Richard Tislow, M.D.
John E. Vance, Ph.D.
Andries Voet, Ph.D.
Peter Vogel, M.D.
John Volkmann, Ph.D.
George Wald, Ph.D.
Roland Ward, Ph.D.
John C. Warner, Ph.D.
T. J. Webb, Ph.D.
Edward R. Weidlein, Sc.D.
John H. Welsh, Ph.D.
Mark D. Welsh, V.M.
E. Clifford Williams, D.Sc.
Leonard George Worley, Ph.D.
Marjorie B. Zucker, Ph.D.

Honorary Life Membership was conferred upon the following eminent scientists:

V. Bjerknes, Professor of Meteorology, Institut d'Astrophysique Théorique, Oslo, Norway.

Niels Bjerrum, Director, Royal Danish Agricultural College, Copenhagen, Denmark.

Niels Bohr, Director, Institute for Theoretical Physics, University of Copenhagen, Denmark.

Sir Henry Hallett Dale, formerly Director of National Institute for Medical Research, Mt. Vernon House, London, England; at present, Chairman of the Board of Trustees, Wellcome Physiological Research Laboratories.

Albert Defant, Director, Institute of Meteorology and Geophysics, Vienna, Austria.

ELECTION OF OFFICERS

The following officers were elected for the year 1948:

For President
HARDEN F. TAYLOR

For Chairmen of Sections
HENRY D. THOMPSON
CLAIRETTE P. ARMSTRONG
SERGE A. KORFF
CHARLES R. SCHROEDER
WILLIAM DUNCAN STRONG
BERNHARD HAURWITZ

For Recording Secretary
GEORGE B. PEGRAM

For Corresponding Secretary
ATHELSTAN F. SPILHAUS

For Treasurer
E. CLIFFORD WILLIAMS

For Editor
ROY WALDO MINER

For Councilors (1948-1950)
ROSS F. NIGRELLI
VICTOR K. LAMER
FREDRICK F. YONKMAN

For Finance Committee
ADDISON WEBB, *Chairman*
CHARLES N. FREY
JOHN A. ZELLERS

PROGRAM OF THE EVENING

After the Business Meeting, the following papers were presented under the heading:

NEW YORK AS THE CROSSROADS IN THE WORLD OF SCIENCE

LEARNED SOCIETIES AND THE EDUCATIONAL ASPECTS OF FUTURE SCIENCE: THE NEW YORK ACADEMY, AND THE SYNTHESIS OF THE SCIENCES

By HARDEN F. TAYLOR
President, The New York Academy of Sciences

FACTORS SHAPING THE FUTURE OF INDUSTRIAL SCIENCE

By GEORGE A. SLOAN
President, The Nutrition Foundation, Inc.

INTERNATIONAL ASPECTS OF SCIENCE

By W. ALBERT NOYES, JR.
Professor of Physical Chemistry, University of Rochester, and President, American Chemical Society

These papers are published on the following pages of this number of the Transactions.

LEARNED SOCIETIES AND THE EDUCATIONAL ASPECTS OF FUTURE SCIENCE

The New York Academy, and the Synthesis of the Sciences

By HARDEN F. TAYLOR*

On February 24, 1817, a group of 21 scientists met at Harmony Hall, Duane and William Streets, New York, signed the constitution, and launched the Lyceum of Natural History on its career. The name was fitting; *Lyceum* reflected the classical education of the time and still prevailing veneration of Aristotle, while *Natural History,* embracing all the descriptive outdoor sciences, was the most advanced branch following Linnaeus, Buffon, Lamarck, and Cuvier. In 1876, the organization changed its name to The New York Academy of Sciences as being more correctly descriptive of its true nature and functions and the much changed course of science. There are only three scientific societies in America senior to The New York Academy of Sciences, *viz.,* The American Philosophical Society of Philadelphia, 1769, the American Academy of Arts and Sciences, Boston, 1780, and the Academy of Natural Sciences, Philadelphia, 1812.

The five counties that now constitute New York City then had a population of 140,000, about that of Yonkers today. The population of the whole United States was a trifle over 9 million, 90 per cent farmers, and considerably less than the population of the New York metropolitan area today, which is about 12 million.

Eight days after the initial meeting in Harmony Hall, James Monroe was to take over the presidency of the United States from James Madison; our war with Britain had ended two years earlier, the Napoleonic wars 20 months before at Waterloo, and the second Peace of Paris, fifteen months before, had settled the issues and launched the western world on the most remarkable and fruitful century in all history, a century marked by only a dozen or so local wars of short duration, and by the flowering of the scientific and industrial revolution which immeasurably elevated the standard of living in material things, enriched and extended the duration of individual life, and made it possible to support, nourish and employ vastly increased populations.

Life in February, 1817, was as yet untouched by the new things to come. There were no railroads; transportation and communication on land was by stagecoach and wagon over muddy roads, at sea by sail, requiring a month to six weeks for a passage to Europe, with salt beef, hard tack, beans and cereal for food on the way (first steam crossing, *Savannah,* March 28-June 20, 1819); there was no way of keeping perishable foods other than drying, salting, spicing, etc., or in cool springs and wells or window boxes in winter for a short time; hermetic canning, although invented in 1810, was not to arrive on this continent till 1840 (in U. S., 1843); all writing and copying was by hand with quills; there was no central heating of houses; the steam boiler was highly explosive and engines without ball governor and Corliss valves, both to follow in 20 to 30 years, were highly inefficient and troublesome; photography had not been thought of; rubber was to be a useless gum for another 22 years before vulcanization; steel making had to await the Bessemer and the open hearth processes for another 40 to 50 years; mechanical refrigeration was equally remote. The first dental college in the world was 25 years away in Baltimore; the practice of medicine was largely in the administration of galenicals, purges, and emetics; anesthesia was another 25 or 30 years in the future; electromagnetism, electromagnetic induction, and the laws of the electric current were yet to be discovered, as were the synthesis of organic compounds, the nature of heat and its mechanical equivalent, and of

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light, the periodic system of chemical elements, the cellular structure of plants and animals, asepsis, bacteria, phagocytosis, immunity, photosynthesis, the extension of astronomy beyond the solar system, and most of our other great scientific laws and generalizations.

Although great things were already in the making, the men of science who were to carry out the remaking of the world were yet to come. Charles Darwin was a lad of 8, and his embarkation on the voyage of the *Beagle* was 14 years in the future; Claude Bernard was 4 years old; Bunsen and Schwann were 7, Louis Agassiz was 10 years old, Matthew Maury 11, Schleiden 13, Liebig 14, and Sir Charles Lyell and Joseph Henry were 20. The arrival of Joule on the scene was to be a year later, Helmholz and Virchow 4 years, Pasteur, Clausius and Gregor Mendel 5, Kelvin 7, Cannizzaro 9, Clerk Maxwell 14, Mendeleev 17, Archibald Geikie 18, Perkin 21, and Willard Gibbs 22.

DuPont's powder factory was working down on Brandywine Creek near Wilmington, but no industrial enterprise had ever given a thought to employing a scientist in order to improve its business. Most of the scientists were men of leisure, some were clergymen, university lecturers, directors of botanical gardens, and a few were busy people such as Franklin had been, who satisfied intellectual curiosity with science as a hobby.

We might almost say, without too much exaggeration, that in 1817 one man with an exceptional I.Q., a highly retentive memory, and willingness to study diligently could know all there was to be known of science of that day.

Such was life in 1817.

I do not need to retell the story of the accomplishments of science during the ensuing century until we entered World War I, in 1917. We select for particular attention for our purposes here the natural and necessary specialization of sciences into more and more and smaller and smaller compartments as knowledge grew, data accumulated and their relationships became more complex.

During that century of progress, many, if not most, of the great accomplishments were achieved each within the framework of its own specialty—the electrical, mechanical, thermodynamic, chemical (both organic and inorganic), and metallurgical achievements were mostly within their own spheres of science.

However, in the latter part of the period, and to a rapidly growing extent, the need has been apparent for more synthesis in the solution of great scientific problems, *i.e.,* bringing to bear on them the knowledge and techniques of two or more and sometimes many of the specialized branches of science. An example was the establishment of physical chemistry.

The multiplication, proliferation, and expansion of scientific effort, the number of men engaged in it, the elaborateness of organization, the expenditure of funds for support, the multiplicity of specialties and their ramification into every remote corner of human interest have now proceeded so far that no man can even conceive or be aware of more than a small part of the total. A few days ago, the list of the scientific publications abstracted in *Biological Abstracts* was sent to scientists in the biological field. It contained 2,313 titles of publications regularly abstracted. The American Chemical Society regularly abstracts about 4,300 publications. If we allow liberally for duplication and for publications enumerated which are only on the fringe of science, we may estimate the number of scientific publications abstracted by the two organizations as 5,000. The two November issues of *Chemical Abstracts* (which appears twice a month) had 519 pages with an average of 10 abstracts per page, or over 5,100 papers for the month, or 61,000 papers per year, and in several languages. In the two Novem-

ber issues of *Chemical Abstracts,* a total of 7,275 authors and co-authors are indexed.

The extremity to which specialization has gone may be illustrated by a review written by J. T. Randall of Maurice Curie's book, *"Fluorescence and Phosphorescence",* in *Nature* for October 11, 1947. Says Randall:

> "The luminescence of vapors, of solutions, of solids, and the phenomena associated with chemi- and bioluminescence all fall within the scope of the subject. Because each of these divisions requires, at any rate to some degree, a different type of background and objective, it is unusual for any one person to apprehend the whole field."

During the later years of our scientific century, it began to appear that many of the major problems awaiting solution had not yielded to attack by specialists (though some of the sciences, such as oceanography, medicine, and geology, were composite sciences all along), and that a concerted attack would be required by convening the efforts of numerous and diversified specialists. The cancer problem is one of these. Numerous others were solved by such organized and concerted effort during the late war. A great many more are and will be before us; indeed, it appears that from now on, more and more of the great problems to be solved will be of the kind which are solved only by concerted effort.

In keeping with the growing need for synthesis of the many sciences in dealing with present problems, the Academy inaugurated a few years ago the Conferences on chosen subjects. These conferences, usually running two days, are designed to bring together from wherever they are the leading researchers on a particular problem, often dealing with it with widely different techniques and from the points of view of different branches of science. The participants come from all over the country and from foreign countries, wherever they may be. The results are usually published as a separate Article of the *Annals.* These conferences have had a gratifying degree of success and are to be continued and increased in number as the Academy's resources permit. They have been, so far, in the fields of medicine, oceanography and meteorology, physiology, nutrition, synthetic organic chemistry, parasitology, pathology of lower animals, psychology, chromatography, animal behavior, physics, and astronomy.

The New York Academy of Sciences is peculiarly well situated geographically and by tradition to serve all the sciences in this way. It is situated in the center of what seems the largest and most concentrated area of scientific activity to be found in the world. If we describe a circle with radius of 50, 100 or 200 miles from where we now are, the circle would contain probably more scientists, and more scientific research and activity, than any other similar area. If we define the area as that accessible overnight by train or two hours by airplane, the cities of Boston, Providence, New Haven, Hartford, Albany, Troy, Schenectady, Syracuse, Philadelphia, Pittsburg, Cleveland, Akron, Buffalo, Rochester, Binghamton, Wilmington, Washington, Baltimore and Trenton, and many other smaller cities, would be included. Within a radius of a hundred miles are colleges and universities of world-wide importance—Columbia, New York, C.C.N.Y., Rutgers, Yale, Vassar, Princeton, Pennsylvania, Fordham, Stevens and Brooklyn Polytechnic, and slightly further away are Pennsylvania State, Brown, Cornell, Syracuse, Amherst, Williams, Connecticut, Harvard, Rochester, Bryn Mawr, Wellesley, Smith, Lehigh and Rensselaer, and many smaller colleges and technical schools. Within the area are the largest number of hospitals, medical and dental centers, and colleges and schools of pharmacy; research institutions—Rockefeller, Merck, Squibb and Warner Institutes of Medical Research, Boyce Thompson Institute of Plant Research, Institute for Advanced Studies at Princeton, Wistar Institute, Nutrition Foundation, Woods Hole Oceanographic Institution, Marine Bio-

logical Laboratory, The American Museum of Natural History, New York Zoological Society, the State Departments of Agriculture, Public Health and Social Welfare of New York, New Jersey and Connecticut—indeed, as we look over the list of such institutions and foundations, it appears impossible to mention all or even the most important ones. We are equally helpless in the mention of industrial corporations who maintain research departments, having such names as Air Reduction, Allied Chemical & Dye, American Cyanamid, American Locomotive, Bakelite, Bell Laboratories, Bendix, Celanese, Ciba, Colgate-Palmolive-Peet, Edison, Fleischmann, General Aniline & Film, General Electric, General Foods, H. Heyden, Hoffman-La Roche, Johnson & Johnson, Metal & Thermit, S. B. Penick, Pfizer, M. W. Kellogg, Roebling, Schenley, Schering, Schieffelin, Socony-Vacuum, Squibb, Standard Oil of New Jersey, Sterling-Winthrop, Union Carbide, U. S. Rubber, Warner, Wellcome Laboratories, Westinghouse Lamp, and literally dozens of others; slightly further away the names of Atlas Powder, Bausch & Lomb, Du Pont, Distillations Products, Eastman Kodak, Hercules Powder, Hooker Electro-Chemical, Leeds & Northrup, R.C.A. Situated in and around New York are also many consulting and service chemical, bacteriological and engineering laboratories, as well as numerous endowed foundations for research in particular scientific fields. New York is also the seat of headquarters for important branches of numerous scientific societies, such as the American Cancer, Geographical, Mathematical and Physical Societies; the Archaeological, Illuminating Engineering, Microchemical, Chemical Industry, Geological Societies; American Immunologists, Industrial Physicians and Surgeons, Orthopsychiatric, Psychiatric, Public Health and Standards Associations; Associations of Child Study, Modern Languages; American Institutes of Mining Metallurgical Engineers, Chemists, Chemical Engineers, Physics, Electrical Engineers; the Institute of Aeronautical Sciences; and many others.

In the midst of this scientific galaxy, the Academy is not only the fourth oldest in the country with its roots in the origins of our scientific era and an unbroken record since: it is now the only scientific society which serves the whole body of science in all its branches here. It has six sections and nine affiliated societies with regular meeting times and places and publishes the *Annals* which began in 1824 and *Transactions* in 1881. For its purposes, it makes no important distinction among the pure or academic, the professional service and the industrial applications of science; they all add to our sum of knowledge and understanding of nature and promote the welfare of mankind.

Throughout its long career, the Academy's size, influence and fortunes have waxed and waned with circumstances of the times. Most of the time it has needed a home; it acquired one in 1835 but lost it by foreclosure of mortgage in the depression of 1844 after a period of inflation somewhat such as we are now having, and it lost its natural history collection in a fire in 1866.

In 1902, the Academy accepted an invitation to make its permanent home at the American Museum of Natural History, including its library which had been moved around from pillar to post for 85 years. In 1926, the library was sold to the Museum.

The 45 years in the Museum have been a happy period, but the arrangement is now no longer suitable. The Academy has outgrown its home in both size and activity. In April of this year, the Council voted reluctantly, but of absolute necessity, to limit the membership for the time being to a total of 4,000 members in the Student and Annual Active Classes. On December 6th, its membership of all classes was 4,009, which is more than ten times the membership in 1935. This membership, representing all 48 states, the District of Columbia, two territories and 28

foreign countries, is at the top level of professional scientists, the vast majority of whom have master's and doctor's degrees, except the juniors who will be among the leading scientists with advanced degrees of the next generation. The space available in the Museum is no longer adequate for the regular meetings of the sections, affiliated societies, and especially for the conferences which are drawing research scientists from all over the country and from foreign countries, to say nothing of the demand for office space. The Museum also has its increasing needs to serve a larger public in a larger city. Our long association with the Museum must therefore come to an end, but when it does the parting will be attended with regrets and pleasant memories especially by the older members of both organizations.

The implications are clear: the only scientific organization representing and serving all the scientists at the professional level in a center of 12 million people immediately at hand and in the center of the world's most active scientific area, in the world's greatest sea port and crossroads of international travel, the new home of the United Nations, and embarked on a new service through its program of conferences in the synthesis of the many sciences as they bear on the larger problems of today and the future, has outgrown its home.

The Academy needs, and must have, a new home.

FACTORS SHAPING THE FUTURE OF INDUSTRIAL SCIENCE

By GEORGE A. SLOAN *

As a measure of self-defense, let me state at the outset that I am *not* a scientist. My experience in life has been largely in industry.

I have been invited here, I presume, because of my interest in the Nutrition Foundation. For the past six years, the Foundation has been carrying on a unique and useful work for the advancement of the science of nutrition through fundamental research. Its entire program is financed by members of the food and related industries.

I have been asked to speak on *"Factors Shaping the Future of Industrial Science."* Perhaps, the Nutrition Foundation provides one example of how industrial science may advance—that is, by industry financing independent basic research in an endeavor to bring forth knowledge which will benefit all mankind, without reference to direct profits to the industry concerned. That, I believe, is one path industry will follow to an increasing degree in the years ahead. Through the creation of greater basic knowledge, industrial science will advance over a broad front. The development of industrial science will come most surely through the nurturing of the search for basic knowledge. Industry must unselfishly support such basic research and, at the same time, be prepared to apply new knowledge.

What is science? For my purposes, it is synonymous with learning and knowledge —guided and checked by the discipline of experimental evidence. Science can trace its history back to the earliest man who began to acquire some knowledge of natural phenomena and the relations between them. When primitive man slowly became conscious, through long observation, of natural occurrences, such as the movement of the heavenly bodies and growth in animal and plant life, we had the beginnings of science. When there was orderly knowledge of some of the natural phenomena, men began to seek the causes of these phenomena and to discuss connections between them. That was the beginning of research.

Soon, men of knowledge began to band together in learned societies to discuss their findings and science really began to grow at an astounding pace. Finally, we find the evolution of scientific investigation as a professional occupation.

Science advances over the road of new knowledge. Therefore, it seems to me that the one factor which will have the greatest bearing on the future of industrial science is research. The importance of research in our modern society has come to be recognized by almost everyone from the industrialist to the politician, and to the man in the street.

The word "research" finds itself on many tongues. It is frequently misused. The interrogator who knocks at your kitchen door to ask what scrubbing brush you use calls himself a researcher. We need to guard constantly against letting the word become distorted and abused. Again, the magic word research is too often misunderstood in regard to the time factor. Let the newspapers announce a grant of thousands of dollars for research in cancer, and the public anxiously awaits on the morrow the announcement of a cure. Too great results are expected too soon.

The rapid growth of industrial research is indicated in the estimates, made by the National Resources Planning Board, that American industry in 1940 was spending over $300,000,000 a year on research, with more than 70,000 research workers in over 2,000 laboratories. Those are pre-war figures. It is probable that since the war they have been greatly increased, but they offer convincing evidence industry has turned to science and research as a factor in prosperity and progress.

Industrial research is necessarily based

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upon a foundation of scientific data and natural laws, making use of the great mass of knowledge accumulated throughout the centuries. Prior to the rise of industrial research, scientific or fundamental research was centered largely in schools, universities and other institutions of learning.

All of the teachings of basic science have, in due time, influenced the course of industrial research, and the principles flowing from the work conducted in university laboratories have served to make possible a large proportion of our industrial development. Thus there has come to be, many believe, an over-emphasis on the achievements of industrial research. Too infrequently do we pause to consider the extent to which applied science has drawn upon so-called pure science for support.

The atom bomb, for instance, which today holds the public imagination, is popularly believed to have been developed solely by intensive research prosecuted under great pressure during the second World War. True enough, it emerged as a device or weapon during that period, but back of the intensive phase of wartime development lay approximately 50 years of patient scientific study and research concerned with atomic structure, radioactivity and energy-mass relationships, all of which combined to chart the course for the eventual achievement. Today, the opportunity exists for scientists to proceed again, perhaps for many more patient years, to discover new knowledge which will, we may reasonably hope, harness nuclear fission to more productive uses than war. That is the penalty and the reward of research—every discovery opens many new avenues for continued investigation and study.

Night after night, most of us are subjected to the flashings of multitudes of neon signs. We are apt to consider them as the discovery of some smart advertising man. We fail to realize that this commercial device is merely the adaptation of scientific studies having to do with the nature of electrical conduction in gases. Had it not been for the basic study of the pressure, volume, and temperature relationships of gases, there would be no neon gas available for exploitation.

The modern vacuum tube is a marvelous device, performing all sorts of services for mankind, contributing in a thousand ways to industrial and social progress. It was perfected by painstaking scientific work in industrial laboratories, but its roots go back to fundamental investigations which were not directed primarily toward commercial application.

Similarly, our modern systems of mechanical refrigeration owe a great debt to the study of vapor pressure and the long and careful development of the laws of thermodynamics which long preceded the clever adaptations that, in due time, translated these matters into everyday servants.

At almost every turn, we find that basic science has provided a well-laid foundation upon which applied science has erected outstanding implements of the modern world. Many of our finest corporations owe their present position of leadership to a far-sighted policy toward scientific research. We have now reached the fortunate stage where we can cite a steadily growing trend to include research in company budgets. This helps to bring the personnel of industrial research groups very close to the fields being explored in our strongest university centers.

The benefit of such a liaison redound upon both groups. Today, however, with the great emphasis placed on research, there is considerable confusion in the minds of the public and of the politicians as to the proper function of research, and how it should be controlled. Indeed, here lies the most dangerous pitfall in the entire picture—the risk that out of an intended measure to develop and strengthen research, political control may gain a disastrous foothold inside the laboratories where men are and should be simply and

sincerely seeking after the truth. It would be better for future generations if the spirit of scientific endeavor could be introduced more widely into political life rather than the reverse.

This situation has not been simplified by the fact that numerous universities are now reaching out into the fields of applied, commercial research, while a number of large industrial laboratories are including a considerable amount of basic scientific investigation in their programs. Meanwhile, the Government is providing increased laboratory facilities for research work on problems of interest both to national defense and public economy, and proposals come before Congress for a tremendous enlargement of Government research activity.

There are many honest differences of opinion as to what kind of research should be continued by universities, Government and industry. Universities, faced with depleted funds, believe they have a logical source of income by commercializing applied research projects. This risk of diverting university research efforts from the more fundamental types of work should be guarded against. The Government, confronted with problems in national defense, has many advisers who sincerely believe it is the duty of the Government to protect the national interest by financing a large program in Government research laboratories. Industry is inclined to work as independently as possible. But this does not imply any desire or need to avoid the fullest cooperation with either university or Government research groups.

In general, all practical applications stem from the progress which is made in fundamental science. If this stream should dry up, the progress of practical application would continue, but the scope would fail to enlarge as it has so consistently done in the past. Hence, it is of vital importance that the universities continue to foster fundamental scientific investigation, because it is only in such an atmosphere that we can rely upon continued progress. It is also to these sources that we must look for the thorough training of the scientists to supply industry with their working forces.

It is important that the search for knowledge be unfettered and untrammeled. Ideas are not made to order nor in accordance with pre-determined schedules. Neither are they nourished by political pressures or by a desire to serve a party interest. If we turn over to Government the major part of our future efforts for the advancement of science, then we deny the effectiveness of our system of free enterprise; we subject science to illogical pressures, and we risk the stultifying effects which can come with too much regimented, Government control.

Industrial research organizations will continue to engage in fundamental studies, usually directed toward the development of new knowledge in fields in which their industries are particularly interested. This is right and proper, and experience has shown it to be useful and valuable. More and more of this kind of work will be done, but it can never be enough. The blank spaces in the pages of knowledge are too vast. Yet, I believe, industry today completely recognizes the need for all of the university types of scientific research that can be provided—the types that provide the building blocks from which many technical adaptations can be made.

Industry knows that the greatest yields of basic science have come from research inspired by a desire to learn the unbiased truth and to roll back the boundaries of ignorance. In times past, our institutions of higher learning have provided an atmosphere in which fundamental scientific research could grow without prejudice. It is the part of wisdom to maintain that favorable atmosphere. Industry more and more will come to recognize its share of responsibility for supporting and maintaining institutions of higher learning.

My faith in that direction arises in no small part from experience with the

Nutrition Foundation. This Foundation was created in 1942 by some of the leaders in the food industry, because they recognized the public responsibility of their industry. They saw, too, that there was a pressing and permanent need for fundamental research. They knew that the food industry was essential to high national production and a high level of national health. They recognized, too, that there was need for a wide degree of freedom in research. They realized that research controlled by specific objectives, or research too closely related to immediate return, would be so limited as to fall far short of the goal.

Thus, the Nutrition Foundation came into being. Its purpose was to carry out a program which was truly scientific, but not to undertake research within its own laboratories. Its method was to finance approved projects in universities and medical centers. Doctor Charles Glen King of the University of Pittsburgh was selected to direct the scientific program. He is aided by an eminent Scientific Advisory Committee, composed of 15 of the most active and critical research leaders in the United States and Canada. This Committee reviews all applications for grants-in-aid and approves all projects. It is this committee which decides what areas of research are likely to bring the most important results, and where the urgency of support exists. In so doing, they accept a responsibility to the science of nutrition as a whole.

The program has had five main long-range objectives, namely:

(1) Research directed toward discovering and measuring the human nutrient requirements.

(2) Research to find how the various nutrients function inside the body and how each can be measured accurately.

(3) Research dealing with maternal and infant nutrition.

(4) Research in which there is direct emphasis upon relationships between nutrition and health.

(5) Education, beyond that provided by research grants, to facilitate the application of new and sound information.

The Foundation has been in operation some six years, which, in the field of science, is hardly more than momentary. Yet it has achieved significant results and contributed to the increased knowledge of nutrition. Let me enumerate a few of the results which have come from Foundation grants:

The determination of adult human protein requirement in terms of essential amino acids.

Appraisal of a new vitamin of the B group important in protecting mankind against anemia.

A more complete knowledge of human milk and cow's milk.

A clearer insight regarding the role of certain hormones in health and disease.

These and many other contributions have been made to the basic science of nutrition and to the well-being of man. How much have they contributed to the applied science of the food industry?

Frankly, I cannot tell. Our responsibility is to basic science. The application of this basic science to the food industry is primarily the responsibility of the scientists in industrial laboratories, and that, I believe, is the way it should be. The Nutrition Foundation, supported by an increasing number of food companies, large and small, applies itself to basic research and publishes the results of its work for those able to put these findings into practical application in whatever area they may be —medicine, education, public health, home economics, or the food industry.

This, I believe, offers a pattern for many other industries to follow. Indeed, it is now being followed in two notable instances. In 1944, the life insurance companies of the United States organized the Life Insurance Medical Research Fund. In January of this year, announcement was made of a new foundation organized by the Pharmaceutical Industry. Both of these organizations are patterned along

similar lines to the Nutrition Foundation, in that funds are provided for basic research grants to universities and medical institutions, and based upon the recommendations of a distinguished Scientific Advisory Committee. Industry knows basic science is best nurtured in universities and institutions of learning, and it will accept responsibility for supporting basic research for the development of both scientists and knowledge. Its support of scientific investigation will not, in my opinion, be closely restricted to its own direct interests. Industry knows that advances in any field of science may well bring it a return. Only recently one of the large oil concerns made a very sizable contribution to a project for broad medical research. That contribution will probably never bring a penny return in increased sales of oil, but it may well bring great returns in the health and happiness of the company's employees and the sound health of the community in which it operates.

I venture to predict that industry will give increasingly of its resources to support the broad cause of higher education. Industry knows that it must look to our universities and colleges for its source of trained and educated manpower. If our standards of higher education are permitted to deteriorate, then the standards of manpower will decline. The problem of financing higher education is today a serious one for hundreds of our independent institutions.

Should the task of the universities be turned over completely to state or federal institutions? I believe not. I believe the American public will see to it that private funds keep our system of higher education reasonably independent of political control. And industry, accepting a broad concept of citizenship, can play an important part in this accomplishment.

INTERNATIONAL ASPECTS OF SCIENCE

By W. ALBERT NOYES, JR.*

Science has become a matter of political as well as economical and social importance, due to the fact that it is essential for the prosecution of modern war. Scientists themselves have not fully recognized the important position that they occupy in the world today, although a minority realize that they have contributed to making war more awful and, through a sense of guilt, have come to believe that it is high time they took a greater interest in the cause of peace.

In their own international relationships, scientists have a common ground which may give them a delusion of having the clue to a peaceful solution of world problems. Even when they do not speak the same language, they often understand each other's symbols and can understand each other's words. It is remarkable how much information one can often obtain from a scientific article written in a language one has never studied. When discussions at scientific congresses leave the purer scientific subjects, one usually finds that scientists have the same weaknesses as other individuals. In the period between the two World Wars, the isolationism of this country was reflected in an apathy toward international scientific organizations, and in most of them this country played a relatively minor role. In attempting international collaboration in matters of scientific publication, national pride prevented working agreements just as effectively as it did in the broad field of international politics.

The situation since the close of World War II has been somewhat better, and there are signs that the scientists of this country have begun to realize that, as representatives of a great nation, they are expected to show some leadership in international scientific organizations. A long history of ineffectual participation makes the progress slow, and it is only fair to state that scientists of other countries are afraid of United States domination just as many other countries fear the domination of the United States in military and political spheres. There are more chemists in the United States than in all of western Europe, and for that reason it is easier to finance publication programs in this country than it is abroad. We often feel that it is more convenient, as well as more efficient, to carry on by ourselves than it is to elicit the cooperation and support of other nations. All too often we forget that actions which appear to us to be for the good of science appear to others to be nationalistically selfish.

International organizations in science have existed for more than 100 years, although they became numerous and effective only after World War I. These organizations have generally had poor financial support, but they have served useful functions in obtaining international agreements on some of the fundamental constants of nature, the atomic weights, symbols and nomenclature. Participation by this country in the various international scientific unions was hampered by lack of funds. Delegates to meetings were chosen mainly among those who happened to be traveling to Europe as tourists, or among a small group of persons financially able to pay their own expenses. This situation still needs rectification, although attempts are being made to develop an informed scientific opinion in this country so that delegates in the future will have some means of knowing the official attitude of American scientists toward the various problems being discussed in these international meetings.

The international organizations which existed before the war were mainly effective among those nations where science was relatively strong, that is, in western Europe and in North America. Other parts of the world had too few scientists and too weak national technical organizations to participate effectively. But the

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role of science in preserving peace must be viewed in a broad light, and hence the various United Nations organizations deserve our attention and support. Several of these deal with scientific problems, such as health, food, agriculture, meteorology, and aviation, but the United Nations Educational, Scientific, and Cultural Organization is the one which deals mainly with pure science. This organization was established formally in Paris during the fall of 1946, although a Preparatory Commission had been surveying the field and developing a program for many months previously. We have not time to give many details of the UNESCO program in science. Since UNESCO covers many disciplines, a certain rivalry has existed, and the attitude of the United States has apparently been one of fear that science would dominate the organization. To some extent, this fear may be justified because scientists are acquainted with each other, familiar with each other's work, and usually have little difficulty in arriving at a program which is very useful and generally accepted. Other parts of UNESCO, such as the ones dealing with education, the humanities, and the social sciences all border on political subjects wherein differences in ideology create problems of a real nature in formulating a program. Thus, it is probably no accident that the section on Natural Sciences of UNESCO has made more real progress than most of the others.

The organizations established after the close of World War I were ineffective largely because they were innocuous. They made scholarly studies in many important domains, but through lack of funds and perhaps, also, through fear of intruding in national fields, they did not become operating organizations. There is a similar tendency evident in the thinking of many persons about UNESCO. Since the problems of the Science Division are relatively concrete, and there seems to be fairly general agreement that UNESCO must do more than make harmless studies, the Science Division has naturally asked for a larger share of the budget than some others are willing to grant. Moreover, it seems to be the philosophy of certain individuals, including several eminent persons in the United States, that every project should be viewed in the light of its effect on the cause of peace. International scientific congresses, exchanges of students and professors, publication of scientific journals, and rehabilitation of scientific laboratories are all worth while in themselves, but one cannot say that a program of that type would ensure peace either in the near or in the long range future. This attitude has given the scientific part of UNESCO's program some real obstacles to overcome, but fortunately, at least for the scientists, other nations give science a more prominent position than does the United States.

Organizations of scientists and contacts between scientists are important for the cause of science. It is essential to have a wide dissemination of scientific information so that techniques, new theories, and experimental facts may be made available to any scientist who can use them. Military security stands squarely in the way of much progress today, although certain restrictions appear to be necessary until more satisfactory agreements have been made in the political sphere. Nevertheless, the impact of science on social and economic problems must be considered. The decision for or against war now lies in the hands of statesmen and will be little influenced by anything a scholar can do in the immediate future.

One sees in the world, today, various forms of government. In this country, we profess to believe in free enterprise, not realizing fully that free enterprise in the broadest sense has become obsolete. When a large fraction of a population works for big corporations or for the government, individual freedom is, to a large extent, circumscribed, and one is dependent on forces beyond any single person's control for gainful employment. Since the stand-

ard of living depends upon rate of production, it is evident that any economic system which causes widespread unemployment has failed to maintain a standard of living as high as possible. In countries with dense populations and with insufficient raw materials, a high standard of living is impossible unless the population is kept busy making things for export which can in turn be used to pay for importation of foodstuffs. Science may aid materially in increasing rate of production in overpopulated countries, but there are countries today which could not possibly attain a standard of living comparable to that which we have in the United States. What products can many of these countries make more economically than Americans can make them? In other words, what could we buy abroad in exchange for the food which other people are forced to receive from us? If raw materials are more plentiful here, and mass production methods have been developed to a higher degree, it seems inevitable that it will take fewer man hours to produce a given quantity of goods here than elsewhere. Aside from a few luxury items, what kinds of goods could we import from western Europe to pay for the foodstuffs we are sending over?

Unless a solution to this problem is found, western Europe will have to be treated as a charity case, and no decrease in tariff barriers or other removals of restraints on trade will provide an answer. Thus, one sees that scientists will be unable to provide anything like a uniform standard of living throughout the world. Unless the standard of living is more or less uniform, there will always be causes for jealousy, friction, and war. Large populations of the world are not going to be content to live in the international poorhouse. The difficulties we encounter are so intimately mixed up with religion, economics, and politics that the scientist must recognize that he alone cannot solve the problem of peace.

Some important steps, however, are possible. Certain countries, including some in western Europe, train only a handful of scientists because the whole system of education is not based on a democratic principle. We have learned one lesson thoroughly in the United States, namely, that for every scientist with new and brilliant ideas, scores and hundreds of less competent but scientifically trained men are essential to do the everyday work and to put new ideas into public use. One Nobel Prize winner, in other words, does not make a country strong. Hence, an important thing for UNESCO or for any other international scientific organization to do, is to broaden the base of education so that each country will be adequately supplied not only with pure scientists but with applied scientists and engineers. Even in countries devoid of great natural resources, much can be done to improve sanitation, provide better housing, and utilize such power sources as do exist. Perhaps, eventually, atomic energy will provide a source of power for those countries lacking coal, oil and water power and unable to export. Sources of power are necessary for a high standard of living.

The program of UNESCO takes into account the need of raising the scientific level throughout the world. Regional Field Cooperation Stations are being established which will aid in the interchange of scientific information. A project in the Amazon Basin may combine research on the utilization of tropical resources with a program of higher education.

We must not, however, confine our attention to applied science. Pure science has its cultural value just as do literature, art, and music. The more we can provide a common basis for culture throughout the world, the better chance we have for mutual understanding and confidence. Science has few equals among the other disciplines in this respect except for one difficulty—the small number of persons who really understand it. Therefore, we make a plea for internationalism in science, not only for the material things it can do in reducing friction by raising the standard of living, but in providing a culture which could be common to all people.

Abstract: ENERGY SOURCES IN GIANT STARS

By DONALD H. MENZEL*
Awarded an A. Cressy Morrison Prize, 1947

The rate of energy generation for the red giants, based on Bethe's carbon cycle and the standard equilibrium models of stellar constitution, is far less than that observed. The alternatives are to abandon either the carbon cycle or the standard model. I have chosen the latter and propose, as a general model for giant stars, one whose atmosphere is greatly distended by dynamical motions. It may even consist of an effective shell, partially detached from the stellar nucleus. The giant stars are thus represented as a sort of compressed planetary nebula, or as a Wolf-Rayet star whose envelope is appreciably denser than the average W-star.

Evidence supporting the validity of this picture includes, especially, Merrill's "symbiotic" stars, like R Aquarii, which simultaneously shows characteristics of a low-temperature long-period variable, a hot star, and a planetary nebula. In this paper, we identify the hot star with the nucleus, the red star with radiations from a partial shell, and the nebula with an external gaseous envelope excited by ultraviolet radiation from the nucleus.

The hypothesis enables one to relate almost the entire range of variable stars, from the Cepheids, through the long-period variables, on to the catastrophic variables.

The paper discusses, in some detail, various theories of atmospheric excitation and support. It is concluded that Kiepenheuer's theory of slowly varying magnetic fields in spots is inadequate to account for the excitation of the corona. However, if there are rapid magnetic variations of small amplitude, the heating effect will take place, as a sort of electrode-less discharge. Such variations, however, will produce radio waves of very low (audio) frequency. Recent experiments by Salisbury and myself have shown that electromagnetic pulsations of this order actually exist at the surface of the earth, though their solar origin has not yet been established.

If such waves do exist, they are a mechanism for cooling a spot. They may well be important for many problems of stellar variation, if stars have spots like the sun. Babcock's recent observations of intense general fields of the stars favor the idea that stellar electromagnetic processes may be fundamental.

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Abstract: THE EFFECT OF *CLOSTRIDIUM TETANI* TOXOID IN THE RELAPSE OF MALARIA

By EUSEBIO Y. GARCIA*

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Over 300 patients, naturally infected with *Plasmodium vivax* and/or *P. falciparum*, were classified with reference to (1) primary or secondary infections, and (2) residence in endemic or non-endemic regions. All received basic treatment consisting of one intramuscular injection of 0.1 gm. of atebrine, followed by either (1) a total of 2.1 gm. of atebrine tablets taken by mouth at five-hour intervals for 7 days, or (2) a total of 3.5 gm. of chloroquine tablets by mouth for the same interval and duration. This treatment removed almost 99 per cent of the asexual stages from the peripheral blood in 20 hours and both asexual and sexual stages at the end of 7 days. This treatment was followed by relapses in 90 per cent of *P. vivax* and 83 per cent of *P. falciparum* patients at an average interval of 115 days.

If, however, 1 cc. of tetanus toxoid is injected subcutaneously at the end of the basic treatment and the same dose is repeated at the end of 3 weeks, none of the *P. falciparum* patients suffered relapses during the subsequent 315 days.

Of the *P. vivax* patients from endemic regions who received atebrine therapy and toxoid injections, 3.35 per cent of those with primary infections and 2.5 per cent of those with secondary infections suffered relapses in the ensuing 315 days.

Of the *P. vivax* patients from endemic regions who received chloroquine medication and toxoid injections, 16.6 per cent of those with primary infections and 6.6 per cent of those with secondary infections suffered relapses in the ensuing 315 days.

Of the *P. vivax* patients from non-endemic regions who received atebrine therapy and toxoid injections, 10.5 per cent of those with primary infections and 6 per cent of those with secondary infections suffered relapses in the ensuing 315 days.

Of the *P. vivax* patients from non-endemic regions, who received chloroquine medication and toxoid injections, 14.3 per cent of those with primary and 16.6 per cent of those with secondary infections suffered relapses in the ensuing 315 days.

These data suggest that patients from endemic areas, as well as those with recurrent infections, have greater resistance and suffer fewer relapses than those who have had less contact with the malarial parasites. Since tetanus toxoid is not specific for malaria, it appears that it exerts its influence against malarial relapses by stimulating and enhancing the immune mechanisms of the body. These mechanisms are cellular in origin and the hypothesis is in accord with accepted immunological theory.

These results probably represent the first successful attempts to inhibit multiplication of protozoan parasites by stimulation of immune mechanisms through a bacterial product.

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